A STUDY ON SERUM URIC ACID LEVELS IN ACUTE MYOCARDIAL INFARCTION

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the regulations

For the award of the degree of

MD GENERAL MEDICINE

GOVT. TIRUNELVELI MEDICAL COLLEGE & HOSPITAL

TIRUNELVELI

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CERTIFICATE

This is to certify that the dissertation entitled **"A STUDY ON SERUM URIC ACID LEVELS IN ACUTE MYOCARDIAL INFARCTION"** submitted by Dr. L. Sivaranchani to the faculty of General Medicine, The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment of the requirement for the award of M.D. degree Branch I (General Medicine) is a bonafide research work carried out by her under my strict supervision and guidance.

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This is to certify that the Institutional Ethical Committee of this College unanimously approves the Thesis /Dissertation/ Research Proposal submitted before this committee by Dr. L.SIVARANCHANI, a **POSTGRADUATE IN GENERAL MEDICINE** in the Department of **GENERAL MEDICINE**, of Tirunelveli Medical College /Hospital, Tirunelveli titled **"SERUM URIC ACID LEVELS IN ACUTE MYOCARIDAL INFARCTION"** registered by the IEC as 111/G.M/IEC/2011 dated. 12.8.**2011**. The Investigator is hereby advised to adhere to all the stipulated norms and conditions of this ethical committee.

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DECLARATION

I, Dr.L.Sivaranchani, solemnly declare that this dissertation titled **"A Study on Serum Uric Acid Levels in Acute Myocardial Infarction"** is a bonafide work done by me at Tirunelveli Medical College from January 2011 to September 2012 under the supervision and guidance of my unit chief, **Prof. Dr.M.Ravichandran M.D.,** Professor of Medicine**.**

This dissertation is submitted to TamilNadu Dr. M.G.R. Medical University, towards partial fulfillment of regulations for the award of M.D. degree in General Medicine.

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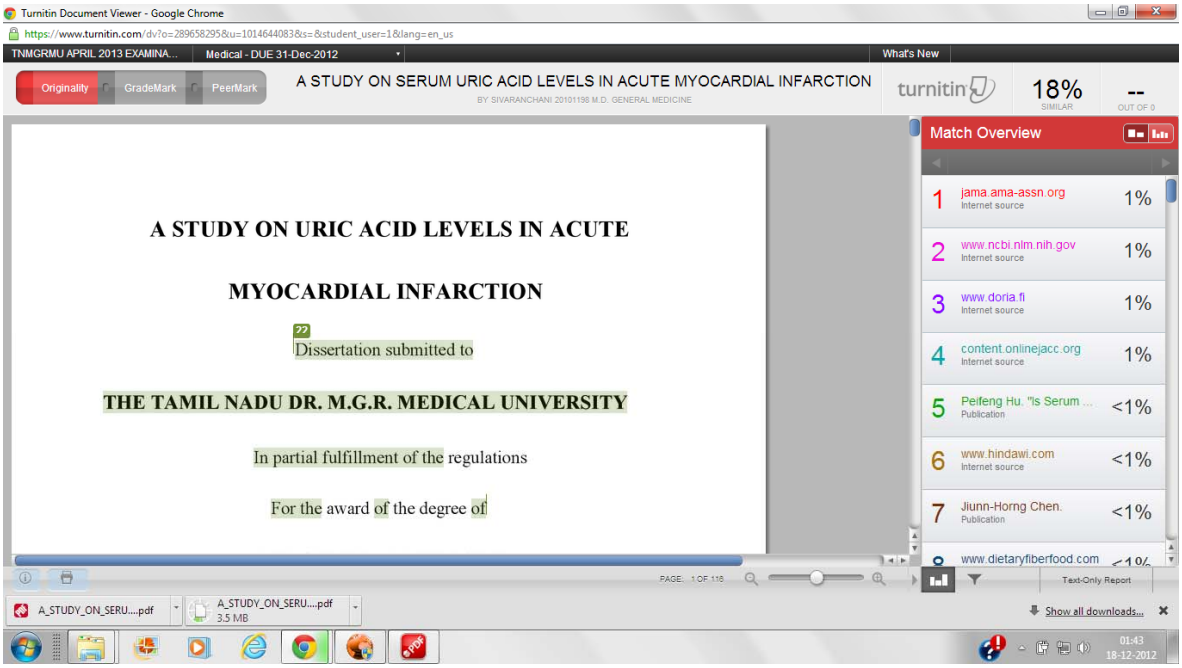
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CONTENTS

INTRODUCTION

Acute Coronary Syndrome is one of the leading causes of mortality in our country. With the increasing incidence of Diabetes and metabolic syndrome, we are encountering more cases of myocardial infarction with increasing severity. For the past two decades, there has been an increasing trend of chronic metabolic diseases globally against a back drop of infectious diseases. This epidemiological transition has been described as three basic stages by Omran : Pestilence and famine, Receding pandemics, Manmade and degenerative diseases. Olshansky[1] added a fourth stage, delayed degenerative diseases.

FOUR STAGES OF EPIDEMIOLOGICAL TRANSITION (TABLE1)

STAGE	PROPORTION OF DEATHS DUE TO CVD	MAJOR TYPE OF CVD
Pestilence &famine	<10%	RHD, Cardiomyopathy due to malnutrition and infection
Receding Pandemics	10-35%	RHD, Hypertension, CAD, Stroke
Degenerative diseases	35-65%	Stroke , CAD
Delayed degenerative diseases	40-50%	Stroke, CAD, Congestive cardiac failure

GLOBAL BURDEN OF CAD [1]

Of the 45 million adult deaths reported in 2002, more than three quarters were due to non-communicable diseases(WHO 2003)[30]. In the twentieth century, less than 10% of deaths were due to coronary artery disease. By the beginning of 21 st century, CAD accounted for almost half of all deaths in the developed world and 25% in the developing world[2]. By 2020, it has been predicted that CAD will claim about 25 million lives annually around the world.

Globally, Ischaemic Heart Disease was the leading killer in the age group >60 years. In adults aged 15-59 years, Ischaemic Heart Disease was the second leading cause of mortality, second only to HIV/AIDS[1].

Although the use of prediction models like the Framingham's study greatly increases the detection of atherosclerotic risk, about 20% of myocardial infarction occurs in the absence of classical vascular risk factors. Many trials have been conducted to identify novel markers and risk factors of atherosclerosis. Similarly, there are only a few clinical predictors of prognosis in acute coronary syndromes (the Killip staging ,TIMI and GRACE scores) . The need for biochemical cardiac markers in predicting major adverse cardiac events (MACE) and mortality has been realized in the recent past. Recent studies have focussed on the prognostic significance of novel markers like hs-CRP, lipoprotein a, homocysteine, BNP, IL-6 and uric acid .

Uric acid is a marker of oxidative stress that reflects the inflammatory process occuring in atherosclerotic plaques and has also been linked to endothelial dysfunction and cell death. It is one of the most studied markers in ACS and other multifactorial diseases like obesity, hypertension, metabolic syndrome and stroke. Studies have ended up with conflicting results, with some studies showing a strong correlation, while others have not demonstrated a clear association. Similarly, a few studies carried out in populations with acute coronary syndrome have shown that uric acid is an independent marker of adverse cardiac outcomes in both short term and long term, while some studies refute it.

In this study, we have focussed on the association of uric acid with various clinical prognostic indicators, major adverse cardiac events(MACE) and mortality in patients presenting with acute ST Elevation MI

AIMS OF THE STUDY

- To assess the prevalence of hyperuricemia in patients with Acute ST Elevation MI
- To study the association of uric acid levels with various risk factors of cardiovascular disease in these patients
- To study the association of uric acid levels with Killip Class, TIMI risk score and adverse cardiac events
- To assess the usefulness of uric acid as an independent prognostic marker of short term mortality in Acute STEMI

REVIEW OF LITERATURE

CAD - TRENDS IN INDIA

In India, CAD incidence is on the rising scale for the past 40 years whereas a declining trend has been noted in the western countries. Mortality due to CAD is expected to rise by 103% in Indian men and 90% in women from 1975 to 2015.(Bulatao and Stephens 1992) .

The Study of Health Assessment and Risk in Ethnic groups(SHARE) has reported a higher incidence of cardiovascular events among South Asians when compared to Europeans and Chinese[3] . Asian Indians are at three times higher risk of CAD than white Americans, six times higher than Chinese and 20 times higher than Japanese.(Ghaffar et al. 2004) . The SHARE study showed that atherosclerosis was higher among Europeans while thrombosis was higher among South Asians, suggesting a thrombogenic profile prevailing among South Asian population[3]. A study in the South East Asian population by Meenakshisundaram et al has brought out that many subjects had an MI even in the presence of low BMI and interestingly, dyslipidemia was not present in most of the studied population[27]. This may be seen in two perspectives: South East Asians have a lower BMI threshold to be called obese. Many other studies have also brought out this fact. Hence the ideal BMI in this population is <23 kg/m^2. People with a BMI of more than 23 may be called overweight and >25 as

obese[27]. This result may also indicate an existing thrombogenic profile in the South East Asian population.

However, the INTERHEART study, one of the largest case control studies, has not proved any ethnic risk factors in South Asians[29]. This study explained that traditional risk factors like smoking, alcoholism, diabetes, hypertension, high waist-hip ratio, dyslipidemia, sedentary life style accounts for more than 90% of CAD events in South Asians.The ICMR study performed in Delhi and Vellore in 1990s reported higher prevalence of CAD in North India[29].

TRENDS IN TRADITIONAL CARDIOVASCULAR RISK FACTORS

Diabetes, hypertension, dyslipidemia, triglyceridemia, metabolic syndrome, smoking , alcoholism, family history of myocardial infarction are the traditional risk factors.

A 35 year trend in BMI, systolic BP and cholesterol has been reported from 199 high income, low income and middle income countries by the Global Burden of Diseases Chronic Disease Risk Factors Collaborating Group[1] from 1980-2005. A trend for increasing BMI was noted in all these countries, with greater rise in high income countries. Mean systolic BP increased in low income countries and dropped in high and middle income countries[4]. Mean cholesterol levels increased in the low income countries and came down in low

and middle income countries. In India , data is similar to that in low income countries.

Epidemiological studies performed in various states have shown that obesity , hypertension, self reported diabetes are common in Kerala and Tamil Nadu, while smoking is common in Mizoram. In India, the cardiovascular risk factors are more prevalent in the urban areas in contrast to the western countries where it is equal in both urban and rural population[29]

NOVEL RISK FACTORS

CRP[5]

CRP has long been recognised as an inflammatory marker and it provides an indirect evidence of the inflammatory milieu of atherosclerosis. Emerging evidence shows that CRP has a direct causal effect on atherosclerosis[31]. CRP binds to oxidized LDL, promoting its uptake by the macrophages in the atherosclerotic plaque , thereby perpetuating the process[5]. hs-CRP levels help us to start statin therapy in high risk individuals. simvastatin reduces CRP levels even before it reduces LDL levels.

LIPOPROTEIN a

Lp(a) is a similar molecule as LDL except for the addition of apolipoprotein --apo(a). It resembles plasminogen[5] in structure and thereby thought to play a role in thrombosis. It also accumulates in atherosclerotic plaques . It binds to thrombin and decreases the fibrinolytic activity of plasmin.

Lp (a) >30 mg/dl increases the cardiovascular risk[5)31]. Niacin is the only available drug that reduces the level of Lp(a).

HOMOCYSTEINE

Homocysteine impairs the production of endothelial nitric oxide, increases the proliferation of smooth muscle cells in the atherosclerotic plaque and activates protein c[5], thereby promoting thrombosis.

FIBRINOGEN

It is a protein synthesized in liver, that activates thrombin, stimulates platelet aggregation, and increases smooth muscle proliferation in the atherosclerotic plaque. Age, menopause, smoking, stress, obesity increases the levels of fibrinogen. Pentoxifylline, omega 3 fatty acids, fibrates, ticlopidine reduces the fibrinogen levels.

MYELOPEROXIDASE

MPO is released during degranulation of leucocytes in an atherosclerotic plaque. It has been shown to predict the 30 day mortality after NSTEMI. Levels of myeloperoxidase increase with endothelial dysfunction. It has been observed that myeloperoxidase is an even stronger predictor of cardiovascular events than CRP[32].

ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE

Experimental results in animals and humans have shown that fatty streak is the initial manifestation of atherosclerosis. This has been increasingly recognised as an inflammatory process resulting in the formation of reactive oxygen species and endothelial damage[50]. LDL particles accumulate within the intima and associate with proteoglycans in the extracellular matrix. This sequestration favours oxidative modification of lipoproteins, which trigger an inflammatory reaction, that results in leucocyte recruitment. The leucocytes exhibit receptors for modified lipoproteins and start ingesting more oxidised lipids and transform into foam cells. As the lesion evolves, smooth muscle cells from the media migrate into the expanding intima and lay down an extracellular matrix there and form an atherosclerotic plaque. In the heart, atherosclerotic process shows a predilection for the proximal left anterior descending artery[50].

PLAQUE RUPTURE

A superficial erosion of the endothelium or a plaque rupture produces a thrombus that occludes the vessel and causes an acute coronary syndrome due to the lack of a well formed collateral circulation. Morphometric studies of these atherosclerotic plaques have shown that macrophages and lymphocytes predominate in these lesions rather than the smooth muscle cells. Patients with active atherosclerotic process and those with acute coronary syndromes exhibit markers of diffuse inflammation(Braunwald), that is, even the atherosclerotic

plaques and endothelial cells remote from the culprit lesion exhibit markers of inflammation[51]. The integrity of the plaque is decided by these inflammatory markers. IFN gamma found in these lesions inhibits the proliferation of smooth muscle cells. Cytokines produced by activated leucocytes increase the formation of proteolytic enzymes that degrade the matrix of the fibrous cap. Thus these inflammatory mediators inhibit the collagen synthesis required for the repair of the eroded fibrous cap and also makes it thin and prone for rupture (hence called the vulnerable plaques). These plaques have a thin fibrous cap and matrix and more inflammatory cells, that trigger thrombotic and fibrinolytic processes, which cause acute arterial occlusion and result in acute coronary syndrome.

This knowledge about pathogenesis of atherosclerosis is very important in identifying newer mechanisms linking it to various risk factors and the ways in which current therapies improve outcomes and in finding out newer therapeutic targets.

ACUTE CORONARY SYNDROME

Patients with ischaemic heart disease fall into two categories : Stable angina and Acute coronary syndromes(ACS). ACS can be subdivided into three groups based on the ECG findings and cardiac markers: ST elevation MI; Non ST elevation MI and Unstable angina. Unstable angina and NSTEMI occur due to plaque erosion or rupture with a non occlusive thrombus. They are usually caused by platelet thrombi (white thrombi) whereas STEMI is usually caused by

fibrin thrombi(red thrombi). When patients present with non ST elevation ACS , cardiac markers are helpful in differentiating unstable angina and NSTEMI. Patients with UA/NSTEMI usually have multiple vulnerable plaques.

Patients with unstable angina and multiple risk factors are at increased risk of developing ST elevation MI. ST elevation is produced by complete occlusion of an epicardial coronary artery. While evaluating a STEMI, we have to consider the temporal phase of the infarction: a) acute phase, lasting from the first few hours to 7 days; b)healing phase- 7 to 28 days ; c)healed phase ->29 days.

CLINICAL CLASSIFICATION OF MYOCARDIAL INFARCTION[5]

(J Am Coll Cardiol 2007)

TYPE 1 – Spontaneous MI related to ischaemia from a coronary plaque rupture or dissection

TYPE 2 – MI due to ischaemia resulting from invreased oxygen demand or decreased supply

TYPE 3 – Sudden cardiac death with symptoms of ischaemia, new ST elevation, or LBBB or coronary thrombus

TYPE 4a – MI associated with PCI

TYPE 4b – MI associated with stent thrombosis

TYPE 5 – MI associated with CABG

FIBRINOLYTIC THERAPY IN STEMI

Fibrinolytic therapy reduces the risk of mortality in STEMI by 50% while administered within an hour of onset of symptoms . When administered early, fibrinolytic therapy reduces the infarct size, limits LV dysfunction, reduces the incidence of complications of STEMI like ventricular septal rupture, arrhythmias and cardiogenic shock. It is proved to be of benefit when administered within 6 hours of onset of symptoms. But still, some patients may

benefit till a period of 12 hours, especially when the pain is persisting or ST segment remains elevated[13]. Patients < 75 years of age attain greater risk reduction with fibrinolytic therapy when compared to older individuals[53].

MAJOR ADVERSE CARDIAC EVENTS

The following are the commonest adverse cardiac events occuring in patients with ST elevation MI[53]:

1. Ventricular dysfunction
2. Pump failure
3. Cardiogenic shock
4. Right ventricular infarction
5. Arrhythmias
6. Recurrent angina
7. Pericarditis
8. Thromboembolism
9. Left ventricular aneurysm
10. Reinfarction
11. Ventricular septal rupture
12. Free wall rupture

ARRHYTHMIAS

Arrhythmias are the most common complications of myocardial infarction. Various rhythm disturbances occuring during MI include ventricular premature beats, accelerated idioventricular rhythm, ventricular tachycardia, ventricular fibrillation, sinus bradycardia,atrioventricular and intraventricular conduction disturbances. Among these, ventricular premature beats are commonly encountered . According to current guidelines , prophylactic anti arrhythmic drugs are contraindicated unless a clinically important ventricular arrhythmia occurs. Beta blockers are ideal in case of frequent ventricular premature beats. Accelerated idioventricular rhythm or slow VT occurs transiently during thrombolytic therapy and is benign and does not lead to ventricular tachycardia[13]. Sinus bradycardia and atrioventricular conduction blocks occurs most commonly in inferior wall MI and may require pacing .

LV FAILURE AND CARDIOGENIC SHOCK

Hemodynamic evidence of LV dysfunction appears when left ventricular contraction is impaired in 20-25% of the ventricle. >40% of left ventricular infarction results in cardiogenic shock[53]. Patients with acute MI and cardiogenic shock usually have triple vessel disease with frequent involvement of LAD. 40% of patients with shock have previous history of MI. Other causes of

cardiogenic shock in MI are right ventricular infarction, ventricular septal rupture, acute mitral regurgitation, cardiac tamponade and free wall rupture.

POST- MYOCARDIAL INFARCTION RISK STRATIFICATION

After diagnosing a myocardial infarction, a physician's goal must be to risk stratify patients, treat complications and to initiate risk factor modification. The following factors help to predict inhospital mortality and recurrent cardiac events

PREDICTORS OF IN HOSPITAL MORTALITY[53]

1. older age
2. tachycardia
3. hypotension
4. Killip class>1
5. Anterior wall infarction
6. Previous infarction
7. LV dysfunction and Heart failure
8. Malignant arrhythmias like supraventricular tachycardia, ventricular fibrillation and ventricular fibrillation
9. Elevated initial serum creatinine
10. Persistent chest pain or early angina on minimal exertion

11. New ST segment changes either depression or elevation
12. Severe coronary artery disease
13. Poor glycemic control
14. Anaemia

AGE

Age is the most important mortality predictor post MI. Older patients are at risk of recurrent MI and the mortality rates are higher in the elderly. More number of older individuals present with atypical symptoms and the risk of bleeding is also high in the elderly, when compared to younger individuals.

KILLIP STAGING

Killip and Kamball described four classes in MI based on clinical presentation and hemodynamic status. This helps to assess the prognosis of patients presenting with MI.

KILLIP CLASS	CLINICAL FINDINGS	MORTALITY
I	No evidence of CCF	5.1%
II	Rales/ raised JVP/S3	13.6%
III	Pulmonary edema	32.2%
IV	Cardiogenic shock	57.8%

TABLE 2

LV FUNCTION

This is the second most important predictor of mortality. Ejection fraction<40% is associated with a poor prognosis. Usually, shock occurs when atleast 40% of the left ventricular mass undergoes infarction[53]. But recent studies have shown that shock occurs due to inappropriate vasodilatation combined with ventricular dysfunction. The raised inflammatory markers and nitric oxide synthase suggest a systemic inflammatory response syndrome that is responsible for sustaining the cardiogenic shock. There are various available options for assessing left ventricular function . These include echocardiography, radionuclide angiography and left ventriculography. No modality has been proved superior to the other but cost and availability are important determinants. Echocardiography is the most commonly used imaging modality.

CARDIAC MARKERS

A few cardiac markers have been found useful in risk stratification of acute MI patients. Among the traditional markers, CK MB has the disadvantage of a short half life, though higher levels are associated with high mortality rates. Troponin, B-type natriuretic peptide and C- Reactive Protein have been found to predict future cardiac events.

OTHER FACTORS

Women have a later age of onset of MI but the mortality rates remain the same in both men and women. Women have higher risk of bleeding.

Patients with diabetes are at a higher risk of death and adverse events , but the treatment in both groups is the same. Anti platelet agents have a consistent or enhanced effect in patients with diabetes.

About 30-40% of the patients with MI have renal dysfunction and is associated with a bad prognosis and increases the risk of bleeding.

RISK MODELS IN ACUTE MYOCARDIAL INFARCTION

Certain risk scores have been formulated using the above mentioned factors to assess the prognosis of the patients presenting with STEMI.They are:

1. TIMI score(Thrombolysis in Myocardial Infarction)
2. The GRACE score (Global Registry of Acute Coronary Events)
3. The GISSI score(Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio

TIMI RISK SCORE IN STEMI[33]

David A. Morrow et al has formulated a simple, bedside, clinical score for risk assessment of ST elevation MI (Circulation 2000;102:2031-2037). This is a useful bedside method of predicting 30 day mortality in patients with STEMI. The risk score includes the following variables(TABLE 3)

SL NO	VARIABLES	SCORES
1	AGE 65-74 YEARS	2
	AGE> 75 YEARS	3
2	SYSTOLIC BP<100	3
3	HEART RATE>100	2
4	KILLIP II-IV	2
5	ANTERIOR STE OR LBBB	1
6	DIABETES, H/O ANGINA/HYPERTENSION	1
7	WEIGHT<67 kg	1
8	TIME TO TREATMENT>4 HRS	1

This risk scoring was derived from patients with ST Elevation MI, eligible for thrombolysis. It has been observed that patients ineligible for thrombolysis were at higher risk of developing adverse cardiac events and hence were excluded from the trials. The 30 day mortality was 44% among those with TIMI score 0 and rose to 77% when TIMI score was more than 8[33]. The maximum TIMI score that can be obtained is 14.

ASSESSMENT OF RESIDUAL ISCHAEMIA

As seen already, severe CAD and recurrent angina are strong predictors of mortality in a patient with myocardial infarction[53]. So submaximal stress testing has been advocated for patients who are not in failure for at least 2 days and without any ongoing ischaemia. This helps to prognosticate patients with

MI. Patients who can ahcieve upto 3 METs carry a good prognosis. Usually exercise stress testing is done but in case of unpredictable ECG pattern like left bundle branch block, baseline ST segment changes or left ventricular hypertrophy, exercise stress testing is contraindicated and we have to go for pharmacological stress testing using dobutamine or adenosine. ACC recommends stress testing within 72 hours of discharge in all patients with uncomplicated infarction[53]. Significant ST segment changes during exercise, hypotension or inability to achieve 3 METS is a sign of poor prognosis and such patients warrant coronary angiography.

ROLE OF CARDIAC BIOMARKERS IN DIAGNOSIS AND RISK SRATIFICATION OF PATIENTS WITH MI

Laboratory evidence of myocardial necrosis is always an integral part in diagnosing and treating acute coronary syndrome. Cardiac biomarkers have been used in conjunction with history and ECG findings in order to confirm the diagnosis of myocardial infarction. An ideal marker has to be specific to the myocardium, sensitive, and quantitative and there should be an early rise in the serum levels of the markers. CPK-MB and Troponin are traditional cardiac biomarkers used at present to diagnose infarction. These markers have certain limitations. As myocardial necrosis is time dependent, these markers may be negative during initial presentation and may later turn out to be positive.

When evaluating a novel marker physicians should consider whether 1.there is a standardized and reproducible assay for the marker of interest; 2.there are consistent prospective studies demonstrating that the given parameter predicts future risk; 3. The novel marker adds to the predictive value of lipid screening 4. There is evidence that it adds to global risk prediction scores like the Framingham's study. Also to be considered is the relative magnitude of novel markers in terms of risk prediction, particularly in comparison to lipid profile. These markers may refine risk assessment and some of them have prognostic significance.

Among the traditional cardiac biomarkers, only troponin has a role in predicting adverse cardiac events. CPK MB has a short half life and is also relatively less specific for myocardial infarction. Certain novel biomarkers, when measured in combination with CK-MB or troponin helps in risk stratification of patients with acute MI[51].

NOVEL BIOCHEMICAL CARDIAC MARKERS[5]

1.MARKERS OF INFLAMMATION

- Hs- CRP
- Myeloperoxidase
- Pregnancy associated plasma protein A,
- Soluble CD-40 ligand

- Interleukin -6(IL-6)
- VCAM , ICAM-1

3. MARKERS OF HAEMODYNAMIC STRESS OR NEUROHORMONAL ACTIVATION

- BNP, NT-pro BNP

4. MARKERS OF VASCULAR DAMAGE

- Creatinine Clearance
- Cystatin C

5. MARKERS OF ACCELERATED ATHEROSCLEROSIS

- HbA1C

6. MARKERS OFTHROMBOSIS & PLATELET ACTIVATION

- Von Willebrand factor antigen
- Plasminogen Activator Inhibitor 1
- Tissue- Plasminogen Activator
- Fibrinopeptide A
- Prothrombin fragment 1+2
- Factors V,VII and VIII
- D Dimer

MARKERS OF INFLAMMATION & OXIDATIVE STRESS

Atherosclerosis is basically an inflammatory disease. Understanding the pathogenesis of atherosclerosis has led to a keen interest on the inflammatory markers that predict the risk of coronary artery disease. Inflammatory markers of atherosclerosis include hs- CRP, lipoprotein (a), homocysteine, myeloperoxidase, soluble CD-40 ligand, IL-6,IL-18 and s ICAM-1 . As already mentioned, atherosclerosis and plaque rupture results in increase in the levels of these inflammatory markers which further create a pro oxidative milieu and makes the plaque unstable[50]. Among the inflammatory markers, CRP is the only proved prognostic marker till now. Myeloperoxidase has shown promising results in various studies and has been tried both as a diagnostic and prognostic marker. According to recent studies, elevated levels of MPO are associated with increased cardiovascular risk even in the presence of normal troponin and CRP levels[5]. Thus MPO may be a more definite marker of future cardiovascular events when compared to Troponin and CRP.

Uric acid is a marker of oxidative stress and inflammation[17]. It has been studied in various populations and many studies have established a strong association of uric acid levels with cardiovascular mortality. A few studies have directly compared uric acid with hs-CRP[26] and have proved a positive correlation between the two markers. Uric acid is basically an antioxidant which turns into a prooxidant under certain circumstances.

BIOCHEMISTRY OF URIC ACID

Uric Acid (2,6,8- trioxypurine- C5H4N4O3) is a weak organic acid that is endogenously produced by purine metabolism[6]. It is formed by the liver and mainly excreted by the kidneys and intestines. RNA and DNA are degraded into purine nucleotides and bases, which are metabolized by the enzyme Xanthine Oxidoreductase into xanthine and uric acid. These steps are irreversible and produce superoxide anions. In lower animals, uric acid is converted to a water soluble product, allantoin by the enzyme uricase and excreted in urine. Man is the only mammal lacking the enzyme uricase[6] (with the exception of the Dalmatian dog), thus having higher levels of uric acid in blood. Nearly two thirds of serum uric acid is produced endogenously while one third is produced from break down of purines. Approximately 70% of urate produced daily is excreted by the kidneys. In the kidney, uric acid is filtered, reabsorbed or excreted by the proximal tubules by the urate/anion exchanger[6], URAT 1. URAT 1 has been identified over brush border membranes of proximal tubular cells and is inhibited by the angiotensin II receptor blocker, Losartan[6].

Normally men have higher uric acid levels when compared to females. Upper limit of normal uric acid levels in men is 5.5 mg/dl[17] while in women, it is 4.5 mg/dl[17]. Uric acid levels increase with age. Pre menopausal women have lower uric acid levels than post menopausal women as estrogen has a uricosuric

effect. Post menopausal females have similar urate levels as that of men. Alcohol causes hyperuricemia through increased lactate production, that competes with uric acid for the URAT transporter[52]. Diuretics lead to volume depletion and decreased absorption of uric acid[7].

OXIDATIVE STRESS & XOR

Reactive oxygen species(ROS) are normal byproducts of aerobic metabolism. In the heart, the potential sources of ROS include xanthine oxidase and NADPH oxidase. According to recent studies, Xanthine oxidase plays a more significant role in the production of ROS when compared to NADPH oxidase. ROS produced by XOR can modulate the activity of various intracellular proteins and signalling pathways including proteins involved in excitation-contraction coupling, such as sarcoplasmic reticulum calcium release channels, ion channels, myofilament proteins and signalling pathways which are coupled to myocyte growth. The modulation of activity of ryanodine receptors and Ca-ATPase result in decreased cardiac contractility. Oxidative stress occurs when production of ROS exceeds the buffering activity of anti-oxidant defence systems, leading to excess of ROS within the cell. ROS may arise secondary to mechanical strain of the myocardium, neurohormonal stimulation or due to inflammatory cytokines.

INJURIOUS STIMULI RESPONSIBLE FOR XANTHINE OXIDASE ACTIVATION AND OXIDATIVE STRESS[7](TABLE 4)

• Angiotensin II • Amylin • Advanced glycosylation /fructosylation end products • Apolipoprotein B • Anti oxidant reserve compromised • Aging • Asymmetrical dimethyl arginine • Free fatty acid toxicity • Lipotoxicity- Hyperlipidemia	• Insulin toxicity • Inflammation • Glucotoxicity • Sorbitol/ Poliyol pathway • Pseudohypoxia(increased NADH/NAD ratio) • Hypertension • Homocysteine • Hs-CRP • Triglyceride toxicity • Uric Acid toxicity – conditional pro oxidant

XANTHINE OXIDOREDUCTASE

Xanthine oxidoreductase (XOR) belongs to the group of molybdenum iron-sulfur-flavin hydroxylase group of enzymes. It is predominantly found in liver, GIT, kidneys, brain and mammary gland[16]. It is also found throughout the cardiovascular system and endothelium bound forms have been described. But

these are 10 to 1000 times lower than the levels found in liver and mammary gland. Expression of these forms are increased in the presence of ischaemia[16] and when there is an increase in pro inflammatory cytokines.

The subcellular location XOR remains controversial till now. In the past, XOR was thought to be entirely cytosolic but researches have shown XOR expression in the rough endoplasmic reticulum, lysosomes and peroxisomes of hepatocytes and in Kupffer and sinusoidal cells

There is about three fold difference in the expression of Xanthine Oxidase activity among individuals. This is due to the presence of various inactive forms like desulfo-XOR. XOR has two interconvertible forms, xanthine oxidase and xanthine dehydrogenase. The major role of xanthine oxidase is conversion of xanthine and hypoxanthine to uric acid. Xanthine dehydrogenase converts NAD+ to NADH. These actions yield hydroxyl free radicals and hydrogen peroxide.

XANTHINE OXIDASE
Hypoxanthine+ H2O+ 2O2 ⟶ Xanthine+ O2- +H2O2
Xanthine+ H2O2+ 2O2 ⟶ Uric acid+ O2-+ H2O2
XANTHINE DEHYDROGENASE
Hypoxanthine+ NAD+ +H2O ⟶ Xanthine+ NADH+ H+
Xanthine+ NAD+ +H2O ⟶ Uric acid+ NADH+ H+

TABLE5

XDH prefers NAD+ as oxidising substrate but is able to react with O2 ,while XO uses only O2(Daria Pasalik et al)[52]

FACTORS THAT REGULATE XOR GENE EXPRESSION(TABLE 6)

POSITIVE REGULATION	**NEGATIVE REGULATION**
Hypoxia Interferon gamma Lipopolysaccharide Interleukin-1 Interleukin-6 Dexamethasone Tumor necrosis factor alfa Prolactin Cortisol	Hyperoxia

Oxygen tension regulates XOR gene expression and also affects the post translational modification of proteins. Studies have shown that xanthine oxidase expression in bovine endothelial cells doubles after exposure to prolonged hypoxia[16]. It has been proposed that hypoxia causes phosphorylation of the enzyme, which increases the enzymatic activity if xanthine oxidase.

The other prime factor that influences XOR expression is nitric oxide levels in the endothelium. Nitric oxide inhibits the expression of XOR

directly[16]. Xanthine Oxidoreductase levels are brought down by the reduction of nitrates into nitrites.

Studies show that xanthine oxidase levels are higher in heart failure and in the recent days has been gaining importance over NADPH oxidase as a source of oxidative stress in these conditions[35]. Xanthine oxidase has also been implicated in intermittent hypoxia induced vascular dysfunction. It has also become an area of therapeutic target.

CAUSES OF HYPERURICEMIA

Under steady state conditions, uric acid production is in balance to its disposal. High levels of uric acid are seen in conditions associated with high cell turn over, enzymatic defects or impaired excretion. Hyperuricemia is a state in which uric acid levels exceed the urate solubility. Uric acid in the blood is saturated at 6.4-6.8 mg/dl at ambient conditions, with the upper limit of solubility placed at 7 mg/dl[17]. In men, hyperuricemia is defined as uric acid level >7 mg% in males, while in females it is > 6 mg%[6]. In children, hyperuricemia is defined as uric acid levels more than 5 mg%.

CAUSES OF HYPERURICEMIA(TABLE 7)

Genetic Causes

Familial Hyperuricemic Nephropathy

Lesch-Nehan Syndrome (HGPRT mutation)

Phospho ribosyl pyrophosphate synthase (PRPPS)mutation

Drugs

Thiazides

Loop diuretics

Calcineurin Inhibitors(Cyclosporine>Tacrolimus)

Pyrazinamide

Low dose Aspirin

Dietary Causes

Diet high in purines(shell fish,organ meats,fatty meats)

Diet high in fructose(high fructose corn sugar, table sugar,honey)

Ethanol

Volume depletion

Hypoxia(tissue or systemic)

Increased cell turn over

myeloproliferative disorders, polycythemia vera

Conditions associated with higher uric acid levels

Renal failure

Metabolic syndrome/Obesity
Untreated hypertension
African American race
Pre eclampsia
Vigorous exercise

Reference:Becker et al. 2005

Long standing hyperuricemia leads to pathological damage to kidney, joints and connective tissue. Hyperuricemia without associated complications is called asymptomatic hyperuricemia. Recent studies have revealed that asymptomatic hyperuricemia is associated with hypertension, metabolic syndrome, dyslipidemia and cardiovascular disease.

BIOLOGICAL ROLES OF URIC ACID

As said earlier, uric acid levels are higher in humans when compared to other mammals. It has been proposed that this confers a survival advantage to humans as increased uric acid levels maintain normal blood pressure in the presence of low salt intake (Watanabe et al). Due to its double bond, uric acid has great anti-oxidant activity and is responsible for more than 2/3 of plasma anti-oxidant activity[18]. This survival advantage has also been linked to the prevention of ageing due to free radical formation (Ames et al). It seems uric

acid and xanthine oxidoreductase may have vast biological roles apart from purine metabolism. Hancock et al has proposed that XOR has anti microbial properties through Nitric oxide dependent mechanism. Breast milk has a high XOR activity which prevents the occurrence of gastroenteritis.

The well established correlation between uric acid levels and atherosclerosis could be a protective reaction (anti-oxidant) or a primary cause (pro-oxidant). This might be due to uric acid being activated against oxidative stress but behaving as a pro oxidant when produced in excess well above normal limits.

Conversely, uric acid may be an indirect evidence of high levels of xanthine oxidase which produces reactive oxygen species. Many hold to the simple concept that serum uric acid in patients with metabolic syndrome, hypertension, type 2 DM, renal failure may reflect a compensatory mechanism to the oxidative stress. However, this does not explain why hyperuricemia is associated with worse outcomes. Some authors have proposed the concept of an anti-oxidant prooxidant switch or urate redox shuttle depending upon the local milieu in the atherosclerotic plaque.[7]

THE ANTI OXIDANT PROOXIDANT URATE REDOX SHUTTLE[7]

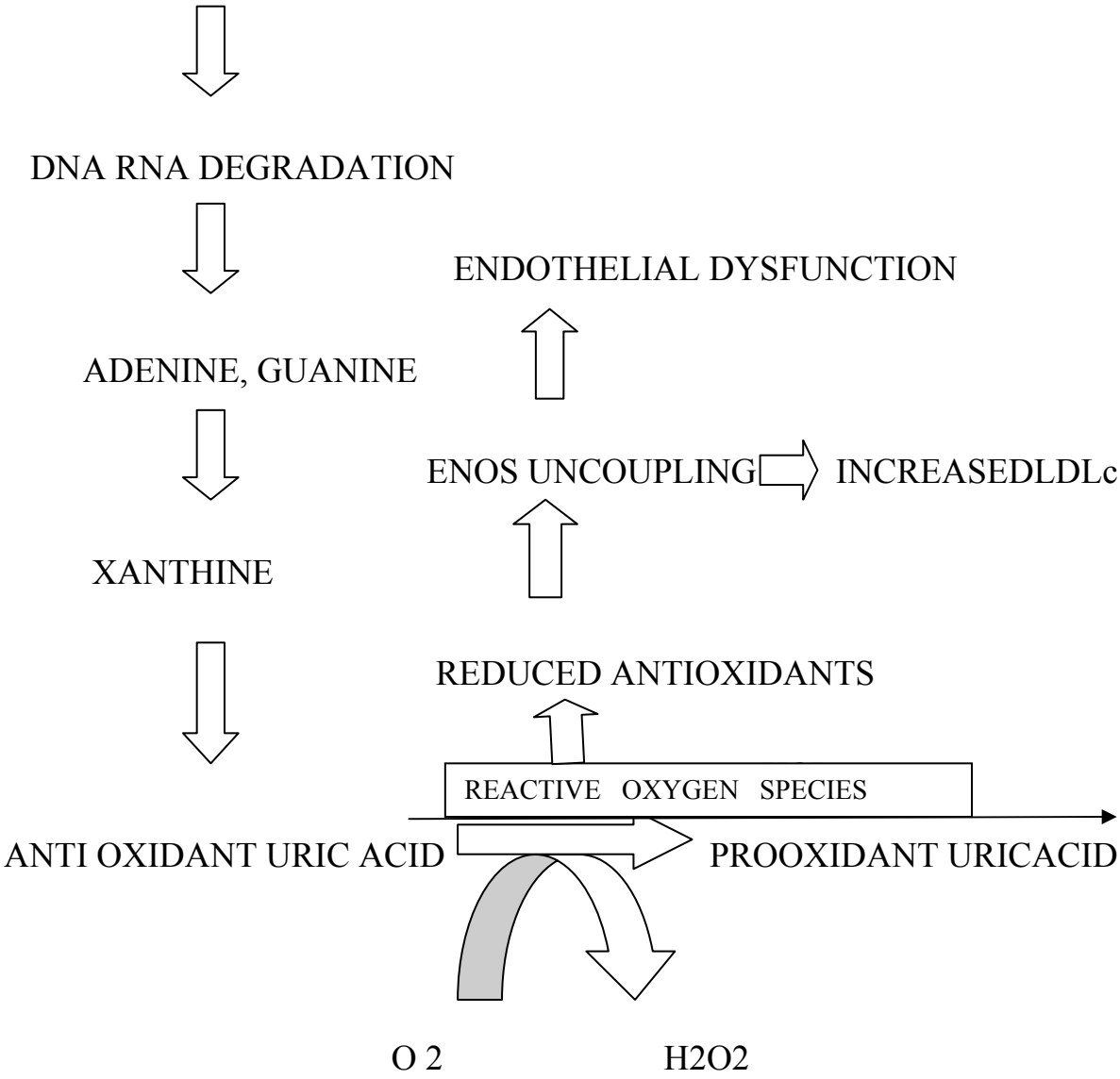
Serum uric acid is an important anti oxidant during the early stages of atherosclerosis and is a major determinant of plasma anti oxidative capacity. However, when the levels reach the upper one-third of the normal limits, it becomes pro oxidant. This is known as the anti oxidant prooxidant urate redox shuttle. This anti-oxidant pro oxidant shuttle seems to depend on its surrounding environment such as timing (early or late in disease process), the surrounding oxidant milieu , location of substrate, acidity, the duration of supply of oxidant substrates and the depletion of anti oxidants. In the atherosclerotic vulnerable plaque, the intima of the vessel has an acidic medium, is depleted of local anti oxidants, and associated with decrease in e NOS production. e NO is a naturally occurring anti –oxidant in the blood vessel. In atherosclerosis, there is decrease in the production of e NO and there is uncoupling of eNOS[7]. This leads to vascular dysfunction. This is also one of the proposed mechanisms for diabetic microvascular complications.

All these processes lead to increased production of purines due to apoptosis and necrosis of the vascular endothelial and smooth muscle cells, thereby increasing uric acid synthesis , allowing it to undergo a prooxidant anti oxidant shuttle.

PROOXIDANT ANTI OXIDANT URATE REDOX SHUTTLE IN AN ATHEROSCLEROTIC PLAQUE(FIGURE 1)

NECROSIS OF VASCULAR ENDOTHELIUM

PRESENCE OF ANTI INFLAMMATORY CELLS IN ATHEROSCLEROTIC PLAQUE



OXIDATIVE STRESS AND ENDOTHELIAL DYSFUNCTION

Oxidative stress contributes significantly to endothelial dysfunction in cardiovascular disease as superoxide radicals readily inactivate nitric oxide which is a potent vasodilator. Nitric oxide and superoxide radicals react at a rate three fold greater rate than the rate at which superoxide dismutase clears O2- (Cai &Harrison)

Endothelium bound XOR inhibits nitric oxide dependent cyclic GMP production in smooth muscle cells thereby impairing vasodilatation(Houston et al.) The role of XOR in oxidative stress and endothelial dysfunction has been confirmed by the isolation of XOR from diseased coronary arteries . It exhibits a negative correlation with endothelium mediated vasodilatation(Landmesser et al. 2002). Local uric acid concentrations are elevated to five to six fold higher in atherosclerotic plaques indicating upregulation of XOR activity[16](Patetsios et al. 2001)

URIC ACID IN METABOLIC SYNDROME

Higher uric acid levels are seen in people with metabolic syndrome. This is thought to be due to the increased production of fatty acyl co A in tissues[23]. This results in the formation of AMP, which breaks down into adenine and then into uric acid. Higher intake of fructose has been implicated in the

pathogenesis of metabolic syndrome. This is because fructose enters the cells, especially hepatocytes and triggers the uninhibited use of ATP for its metabolism by fructokinase. ATP depletion results in lactic acidosis and resultant hyperuricemia[52]. Due to the excessive use of ATP, synthetic processes are triggered, especially triglyceride levels are raised[23]. Studies have shown that measures that decrease triglyceride levels are associated with decrease in uric acid levels. Hyperinsulinemia reduces the excretion of uric acid and thereby induces hyperuricemia in metabolic syndrome[52].

SERUM URIC ACID LEVELS IN HYPERTENSION

Disturbances in renal function is one of the major mechanisms involved in the pathogenesis of systemic hypertension. Any disturbance in the function of URAT transporters, polymorphisms of genes associated with these transporters and reduced glomerular filtration rate are the main causes of hyperuricemia in hypertension[23]. It has also been postulated that uric acid causes tubulointerstitial disease of the kidneys in hypertensive patients leading to salt dependent hypertension[23]. Hypertension also induces microvascular renal injury and causes an increase in lactate levels, which in turn leads to hyperuricemia[52]. In essential hypertension, there is alteration of renal handling of sodium, leading to increase in mean arterial pressure and decrease in renal blood flow, thus leading to decreased excretion of uric acid.

URIC ACID AND DYSLIPIDEMIA

Higher uric acid levels have been observed in persons with high waist hip ratio. In these subjects uric acid levels show a linear correlation with the plasma levels of leptin produced by the adipose tissue. Triglyceride levels have a significant association with hyperuricemia. This is because Triglyceride synthesis in the liver is associated with increased requirement of NADPH and it also accelerates purine formation, leading to hyperuricemia[23]. Some studies show a negative correlation of uric acid with HDL.

URIC ACID AND CARDIAC DISEASE

Uric acid first gained medical importance when it was discovered by Garrod as the cause of gout. About 50% of patients with gout had hypertension, one quarter suffered from renal disease, and majority developed cardiovascular disease. Subsequent researches proved its association with hypertension, atherosclerosis, renal disease and stroke.

In 1951, Gertler et al proved that uric acid levels are much higher in hospitalised CAD patients when compared to patients hospitalised due to other diseases[17]. Uric acid has also been identified as a risk factor in the recent past. It has been found that uric acid increases platelet aggregation, reduces nitric oxide production and causes endothelial dysfunction, raises the levels of oxidised LDL and promotes atherosclerosis[37]. But the fact whether uric acid is a causative factor or just a risk marker remains unknown.

One particular study has proved that uric acid levels along with left ventricular mass estimation is a strong predictor of future cardiovascular events like angina, myocardial infarction, congestive cardiac failure and even cerebrovascular event. In a study conducted in China, Chang-Fu Kuo et al have brought out association of hyperuricemia with increase in arterial stiffness and the development of cardiac hypertrophy[14].

Uric acid levels show a linear correlation with cardiovascular mortality in patients with heart failure. This has been linked to endothelial dysfunction and mechanoenergetic uncoupling (increase in energy consumption while cardiac work decreases), which lead to increased formation of lactate. Lactate competes with uric acid for the URAT transporter and hence leads to hyperuricemia. Patients with heart failure have very low levels of Superoxide dismutase ,while the XOR acttivity is enhanced to >200% in the endothelium. Allopurinol has been proved to increase myocardial contractility and decrease the demand of the stunned myocardium in animal studies.

Hyperuricemia has also been linked to ischaemia-reperfusion injury that occurs in myocardial infarction[16]. Though the precise mechanisms have not been determined yet, the increase in substrates for the enzyme XOR during ischaemia appears to positively regulate XOR expression. XOR levels are found to be eight times elevated in aortic endothelium after reperfusion following ischaemia.

MAJOR STUDIES THAT STUDIED ASSOCIATION OF URIC ACID WITH CARDIOVASCULAR OUTCOMES (TABLE 8)

SLNO	STUDY	RESULTS
1	THE NHANES I EPIDEMIOLOGIC FOLLOW UP STUDY	Serum uric acid levels predicted cardiovascular mortality in both males and females even after adjustment for age and race and this association was well pronounced in post menopausal females
2	THE FRAMINGHAM STUDY	A prospective study conducted on whites which proved no significant association between uric acid levels and cardiovascular mortality when adjustments were made for age, race and other covariates
3	THE LIFE STUDY	Serum uric acid levels had significant association with incidence of cardiovascular events in high risk hypertensive subjects
4	THE PIUMA STUDY	Serum uric acid levels in highest quartiles were associated with higher incidence of fatal cardiovascular events and all cause mortality
5	KOJIMA ET AL	A metaanalysis of nine prospective studies in patients with acute myocardial infarction that found a significant association between uric acid levels with age, Killip class and cardiovascular mortality

STUDIES OF URIC ACID IN CARDIOVASCULAR DISEASE AND OUTCOMES

There are two large studies regarding the role of uric acid in cardiovascular disease and outcomes.

THE NHANES 1 EPIDEMIOLOGIC FOLLOW UP STUDY[44]

The NHANES 1 Epidemiologic Follow up Study(1971-1987) indicated that baseline serum uric acid was an independent predictor of mortality, particularly of cardiovascular death, but only in women. But another large cross sectional study, the Framingham's Study reported that the apparent relationship of uric acid to cardiovascular mortality was not sustained. The authors concluded that the use of diuretics reduced the statistical significance of serum uric acid to cardiovascular outcome. So in order to prove the unresolved correlation between uric acid levels and cardiovascular mortality, the NHANES I epidemiologic follow up study was extended to a period of five years from 1987 to 1992. This nearly doubled the deaths available for study in the sampled population.

The total NHANES 1 sample included 20729 persons, aged 25 to 74 years. Low income persons, women of child bearing age, the elderly were oversampled. Subjects were excluded if they had myocardial infarction , gout, stroke, or were pregnant at the baseline. Of the total sample, a subsample of 6913 subjects called the detailed sample was analysed in greater depth. Follow

up data was collected in four series of follow up. Death was analysed for all causes and ischaemic heart disease.

Of the total deaths, 45.9% were due to cardiovascular disease. It was observed that uric acid levels predicted the cardiovascular mortality of both men and women older than 45 years of age whereas it did not predict the outcome in younger individuals. In menopausal women, the predictive value of uric acid remained significant even when it was adjusted for post menopausal status. Subjects who were on diuretics and alcoholics(consuming alcohol more than twice per week) had higher uric acid levels when compared to others. In women using diuretics, the risk of cardiovascular mortality for a similar increase in uric acid level was higher when compared to those not on diuretics. In men with cardiovascular risk factors and those on diuretics, no significant association was obtained between uric acid levels and cardiovascular mortality. Even in persons with no traditional risk factors, high uric acid levels predicted mortality. These results were similar to that obtained in a previous NHANES study that was extended into this study.

THE FRAMINGHAM'S STUDY[39]

The total population included in the study was 6763 . Similar to the previous study, risk factors were noted and the subjects were followed up for 23 years. The total deaths were 1560 and cardiovascular deaths were 617. The uric acid levels were higher in all age groups of men when compared to women.

Among men, high serum uric acid was associated with decreased mortality. This study found no significant correlation between serum uric acid levels and cardiovascular mortality or incidence of cardiovascular events after adjusting for age, diuretic use , diabetes and other factors. Higher uric acid levels were significantly associated with diuretic use. But the limitation of this study was that it studied majority of white people. This result cannot be extrapolated to other population. The socioeconomic groups were not taken into consideration.

NHANES vs FRAMINGHAM'S STUDY

As mentioned previously, the study population was heterogenous in NHANES study, while it contained predominantly whites in the Framingham's study. The mean age group was higher in the NHANES study and increasing age was one of the determining factors of cardiovascular mortality. NHANES showed a significant correlation of uric acid with cardiovascular mortality even in the whites.

STUDIES THAT ASSESSED URIC ACID LEVELS IN ACUTE CORONARY SYNDROMES

Vladimir Trkulja[8] et al has performed a meta analysis of nine studies conducted in patients with acute myocardial infarction and has proved the association of uric acid levels with cardiovascular mortality. Out of the nine studies, six were conducted in patients with STEMI who underwent PCI and three in mixed population of acute myocardial infarction. The outcomes studied were mortality and occurrence of major adverse cardiac events. Short term (upto 30 days) and medium /long term outcomes were studied. There was a significant association between higher uric acid levels and major adverse cardiac events and short and medium/long term mortality.

The limitation of this study was that some studies were retrospective. No study matched the normouricemic and hyperuricemic subjects with respect to age, Killip class, or renal function. Age > 65 years, Killip class>II/III and renal insufficiency were the most important predictors of mortality in acute myocardial infarction. Uric acid levels significantly correlated with these factors.

MATERIALS AND METHODS

STUDY DESIGN

This is a prospective study conducted on a sample South Indian population admitted in the department of Cardiology during the period of 2011 to 2012. The study included a standardized questionnaire and examination, based on which patients were included in the study. A total of 152 subjects admitted with ST elevation Myocardial Infarction were analysed and among them, patients with evolved MI, prior history of myocardial infarction, renal disease, and those on diuretics and aspirin, were excluded. The total sample population included in the study was 75 patients, aged 24 to 75 years. The study population included 65 males and 10 females.

INCLUSION CRITERIA

1. Acute ST elevation MI, defined as

Classical anginal pain within the prior 12 hours associated with either

A) STsegment elevation in atleast two contiguous leads, greater than 0.1 mV in limb leads or greater than 0.2 mV in precordial leads

B)New or presumably new left bundle branch block.

EXCLUSION CRITERIA

1. Patients with chronic kidney disease
2. Evolved MI
3. Patients with contraindications to thrombolysis
4. Prior history of coronary artery disease
5. Chronic alcohol intake/ Binge drinking in the past one week.
6. History of aspirin/ diuretic intake
7. Patients on Anti Tuberculosis Treatment
8. Gout
9. Presence of myeloproliferative diseases
10. Pregnancy
11. Hypothyroidism
12. Patients on calcineurin inhibitors.

METHODS

A detailed history was elicited regarding duration of chest pain, nature of chest pain, associated symptoms, previous illness and medications, presence of risk factors like diabetes, hypertension, smoking, alcoholism, family history of MI , and a detailed clinical examination was done and patients were categorised into Killip class I to IV. The window period was noted and patients with acute MI and a window period of less than 12 hrs were thrombolysed with

streptokinase 1.5 million units. Any complication occurring during thrombolysis was made note of. Continuous cardiac monitoring was done for all patients atleast during the initial three days and prolonged if complications occurred.

On admission, routine investigations like blood sugar , urea, creatinine, complete blood count were done and serum uric acid level was estimated. Total cholesterol and triglyceride level was also estimated on the day of admission. Fasting and post prandial blood sugar was estimated in all patients. Diabetes was defined as fasting blood sugar >126 mg% or post prandial blood sugar>200 mg% or euglycemia with the use of insulin or oral hypoglycemic agents. Body mass index was calculated as weight in kg/ height in m^2 and TIMI risk score for STEMI was calculated for all patients on admission (table 4).

Serum uric acid level was reestimated on day three. Echocardiography was done on the fifth day and ejection fraction was assessed. Patients were followed up till their discharge or till one week whichever was longer. Any complications or mortality occurring during this period were also noted. Adverse cardiac events included arrhythmias (excluding benign premature beats and Idioventricular rhythm occuring during thrombolysis), sudden cardiac arrest, shock, cardiac failure, ventricular septal rupture, papillary muscle dysfunction, free wall rupture, reinfarction and pericarditis. Other complications like bleeding episodes, cerebrovascular accident and acute kidney injury were also taken into account.

STATISTICAL ANALYSIS

Data analysis was done and subjects were divided into two groups: one group had patients with normal uric acid levels and the other had patients with hyperuricemia. Serum uric acid levels between the two groups on day one was compared by Students unpaired 't' test and within the groups on days one and three was compared by paired 't' test. The continous variables like age, window period, lipid profile, BMI, TIMI score were compared by unpaired 't' test. The categorical variables like sex, Killip class, diabetes, hypertension, smoking , lipid profile, complications and mortality were compared between the two groups by χ^2 (Chi-square) test, Odd's ratio and Z test of proportions wherever applicable. The statistical package IBM SPSS statistics -20 was utilized for analysis and interpretations. The P- values less than 0.05 ($P<0.05$) were considered as significant in two tailed condition.

RESULTS AND OBSERVATIONS

The study population had 75 subjects in the age group of 21 to 80 years. The mean age of the total population was 56.80 years.

AGE DISTRIBUTION IN STUDY POPULATION

TABLE 9

AGE	21-30	31-40	41-50	51-60	61-70	71-80
MALE	2	5	7	26	17	5
FEMALE	0	1	1	3	8	0

SUA IN mg/dL	AGE IN YEARS					
	21-30	31-40	41-50	51-60	61-70	71-80
3.1-5.0	0	5	2	6	0	0
5.1-7.0	2	1	5	12	10	1
7.1-9.0	0	0	1	11	10	4
>9.0	0	0	0	0	2	3

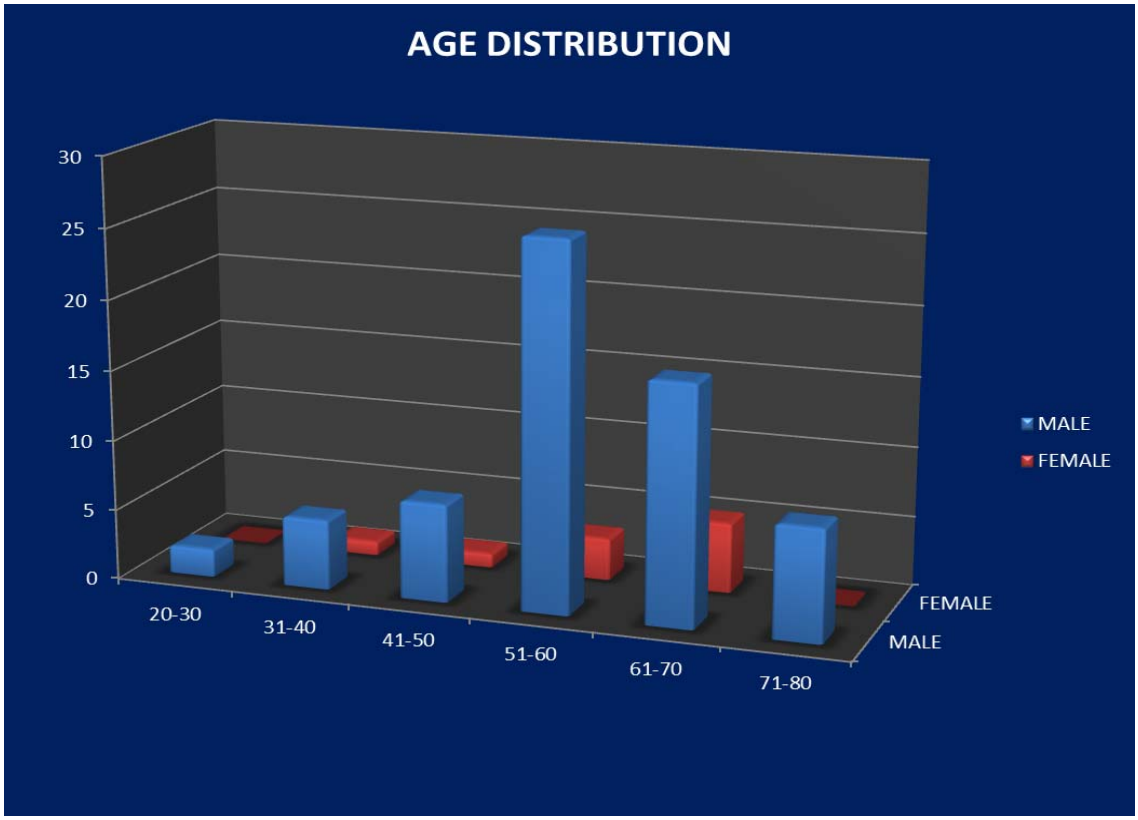


FIGURE 2: The mean age of the total population was 56.80 years. Men had a mean age of 57.55 years and the mean age in women was 66.04 years.

MEAN URIC ACID LEVEL IN DIFFERENT AGE GROUPS (TABLE 10)

AGE	**21-30**	**31-40**	**41-50**	**51-60**	**61-70**	**71-80**
MALE	5.9	4.58	5.8	6.28	7.86	8.24
FEMALE	-	4.2	5.2	5.7	6.48	-

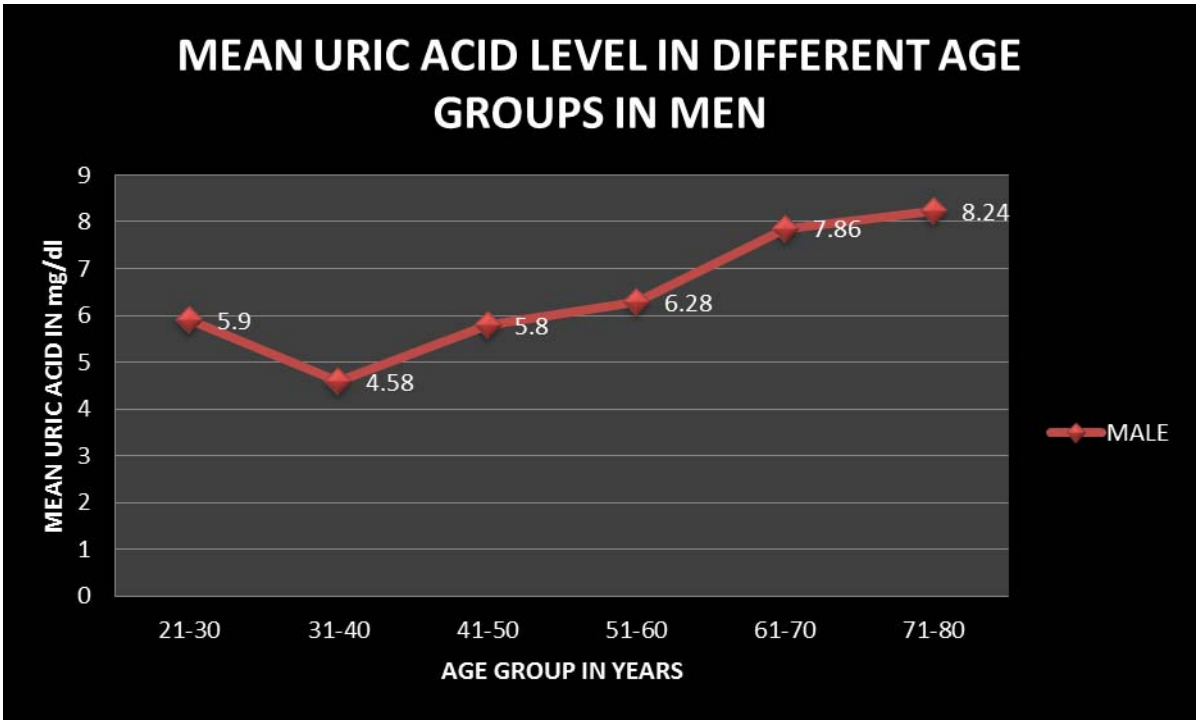


FIGURE 3

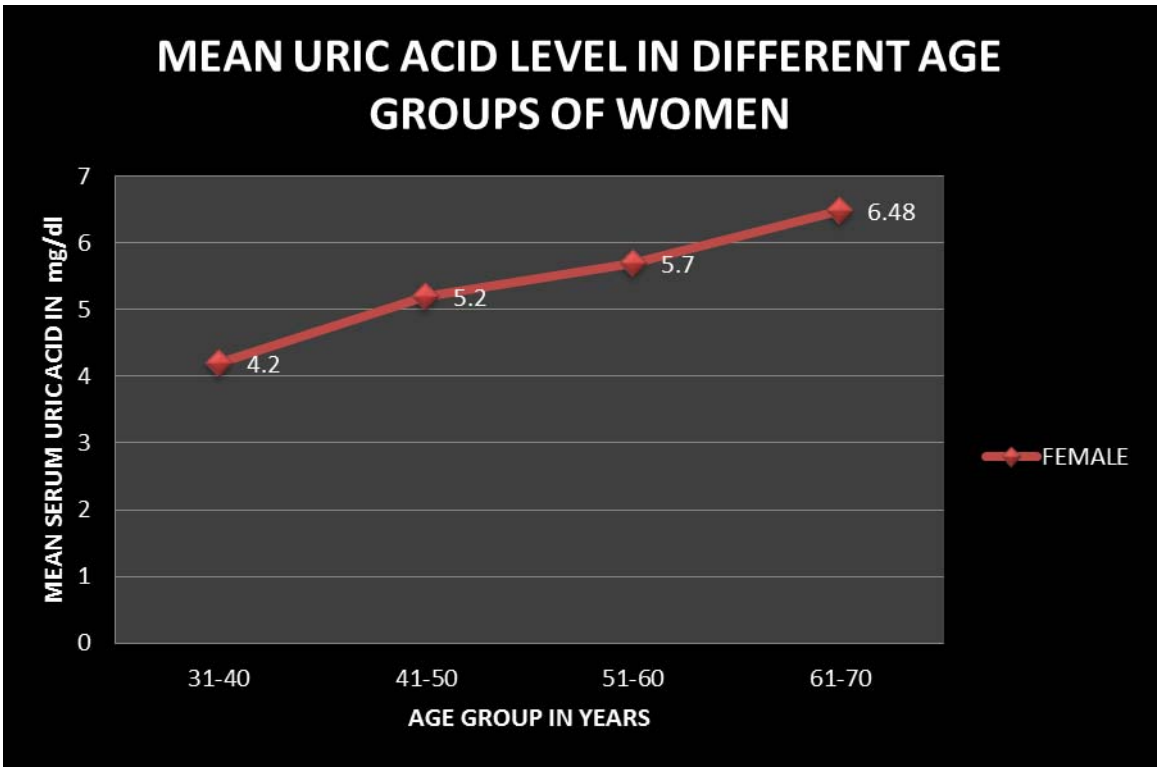


FIGURE 4: Uric acid levels increased with age in both males and females

Comparison of Hyperuricemia and Non-Hyperuricemia cases according to age (Table 11)

Variables	Hyperuricemia		Non-Hyperuricemia		Difference B/W H & NH	't'	df	Sig.
	Mean	SD	Mean	SD				
Age (years)	64.2	7.2	50.8	10.9	13.4	6.297	73	P<0.001

Age differed significantly between the two groups($p<0.05$). Uric acid levels were higher in older individuals.

SEX DISTRIBUTION

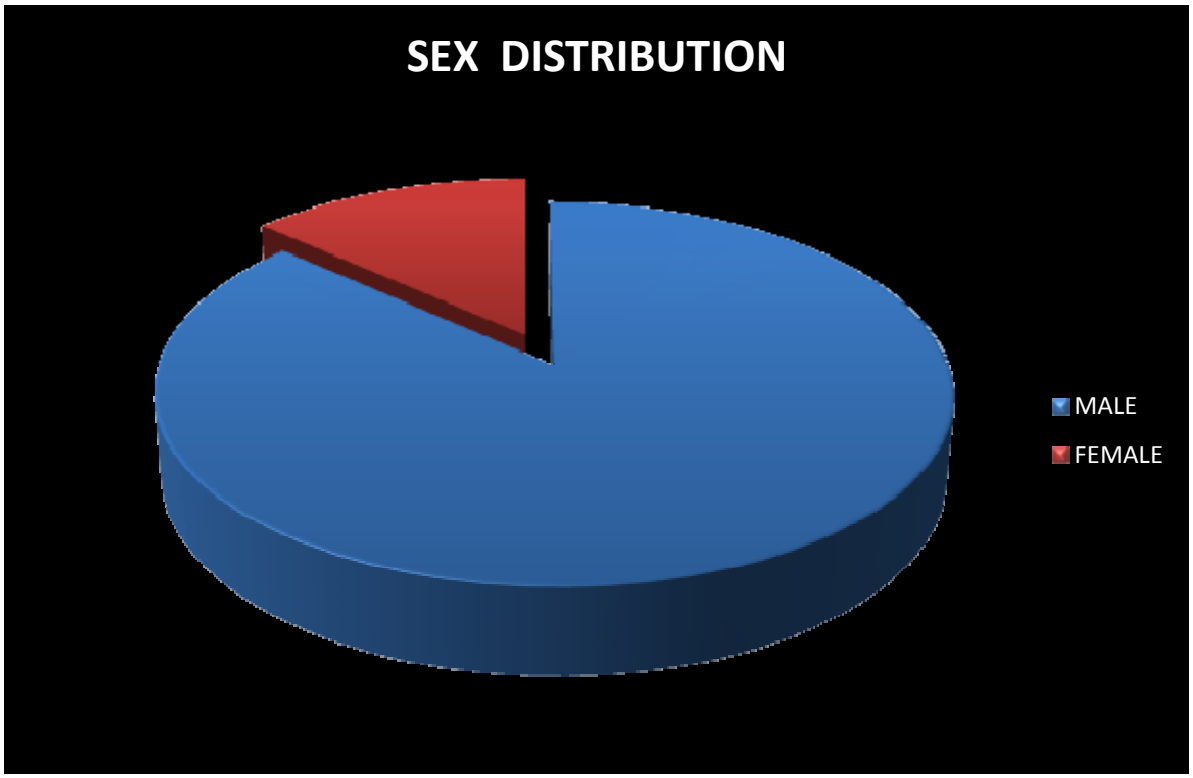


FIGURE:5: The studied population had 87% males and 13% females.

PREVALENCE OF HYPERURICEMIA IN THE STUDY POPULATION

(TABLE 12)

SEX	NORMAL URIC ACID	HYPERURICEMIA
MALE	32	33
FEMALE	4	6

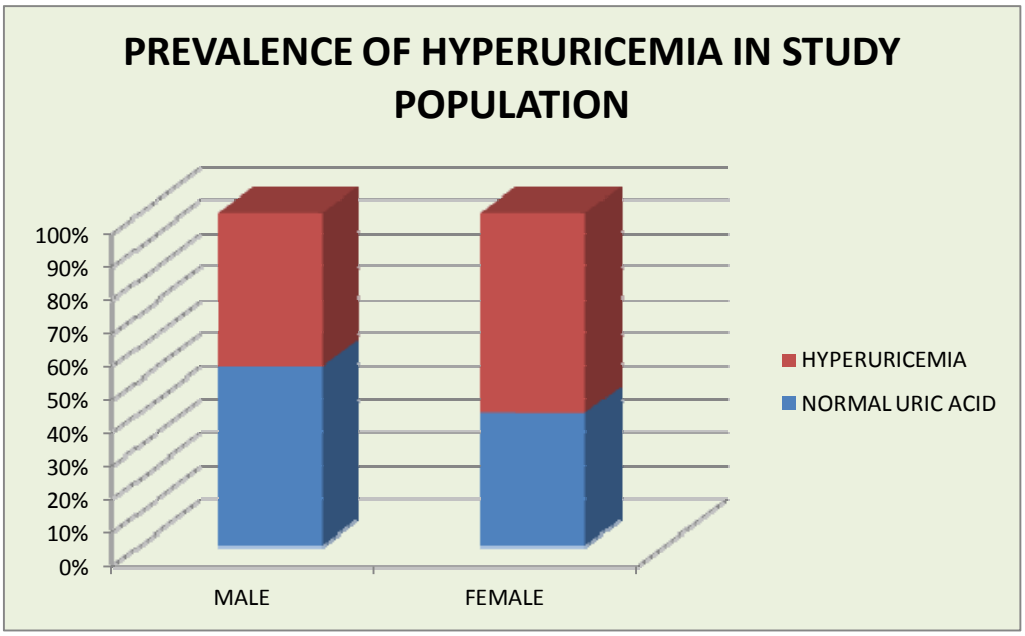


FIGURE 6: The prevalence of hyperuricemia was 50.77% in men and 60% in women.

DISTRIBUTION OF URIC ACID LEVELS IN MALES AND FEMALES

(TABLE 13)

SEX	SERUM URIC ACID IN mg/dl			
	3.1-5.0	**5.1-7.0**	**7.1-9.0**	**>9.1**
MALE	12	23	25	5
FEMALE	1	8	1	-

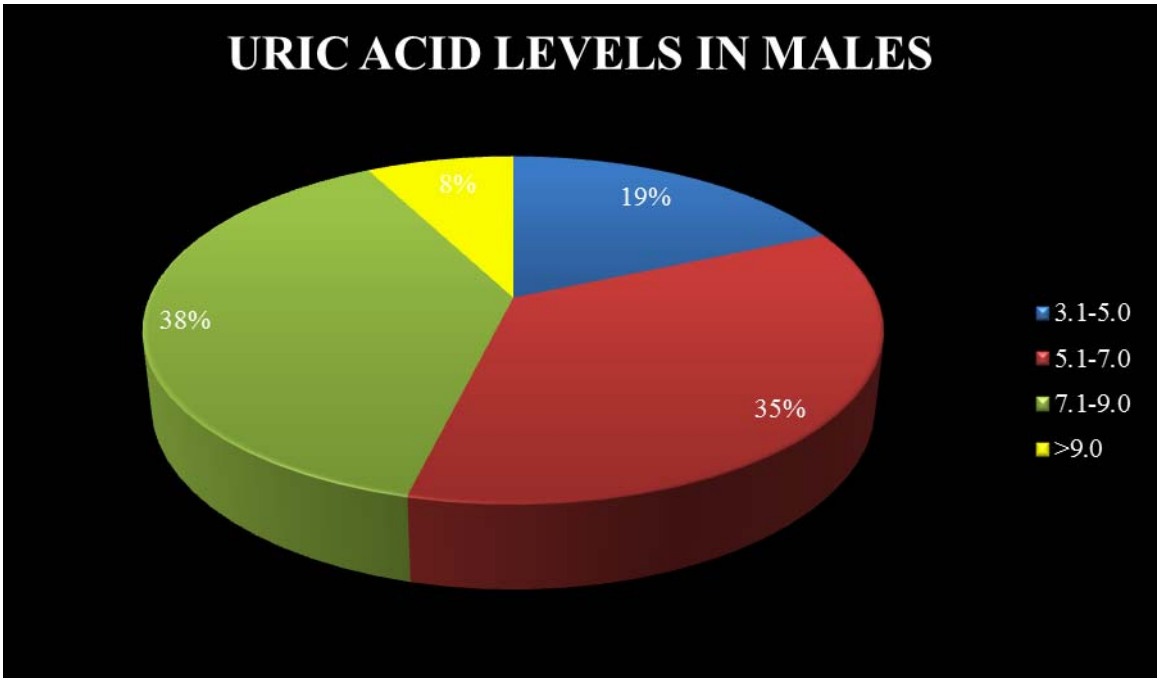


FIGURE 7: Mean uric acid level in the studied population was 6.31mg%. Men had relatively higher uric acid levels when compared to females.(mean – 6.74 mg%)

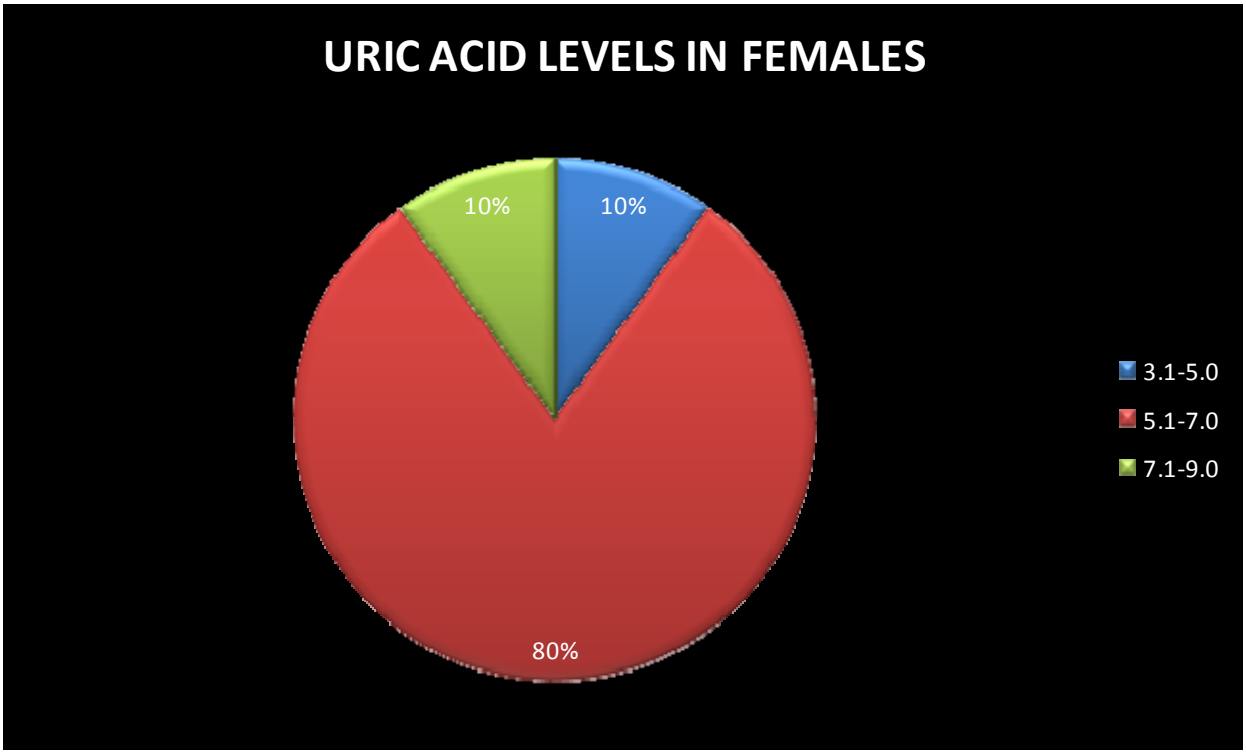


FIGURE 8: The mean uric acid level in females was 5.49 mg%

Table-14. **Association between serum uric acid and gender**

Genders	**Acute STEMI Sr uric acid**			χ^2	**df**	**Sig.**
	Hyper	**Non Hyper**	**Total**			
Male	33	32	65	0.296	1	P>0.05
Female	6	4	10			
Total	39	36	75			

The Table 14 shows the association between serum uric acid with genders of STEMI. The gender did not have any significant association with Sr. Uric Acid (P>0.05).

TYPE OF MI DISTRIBUTION IN STUDY POPULATION

TABLE 15

SEX	TYPE OF MYOCARDIAL INFARCTION			
	AWMI	ASMI	IWMI	LBBB
MALE	29	14	19	3
FEMALE	1	3	6	0

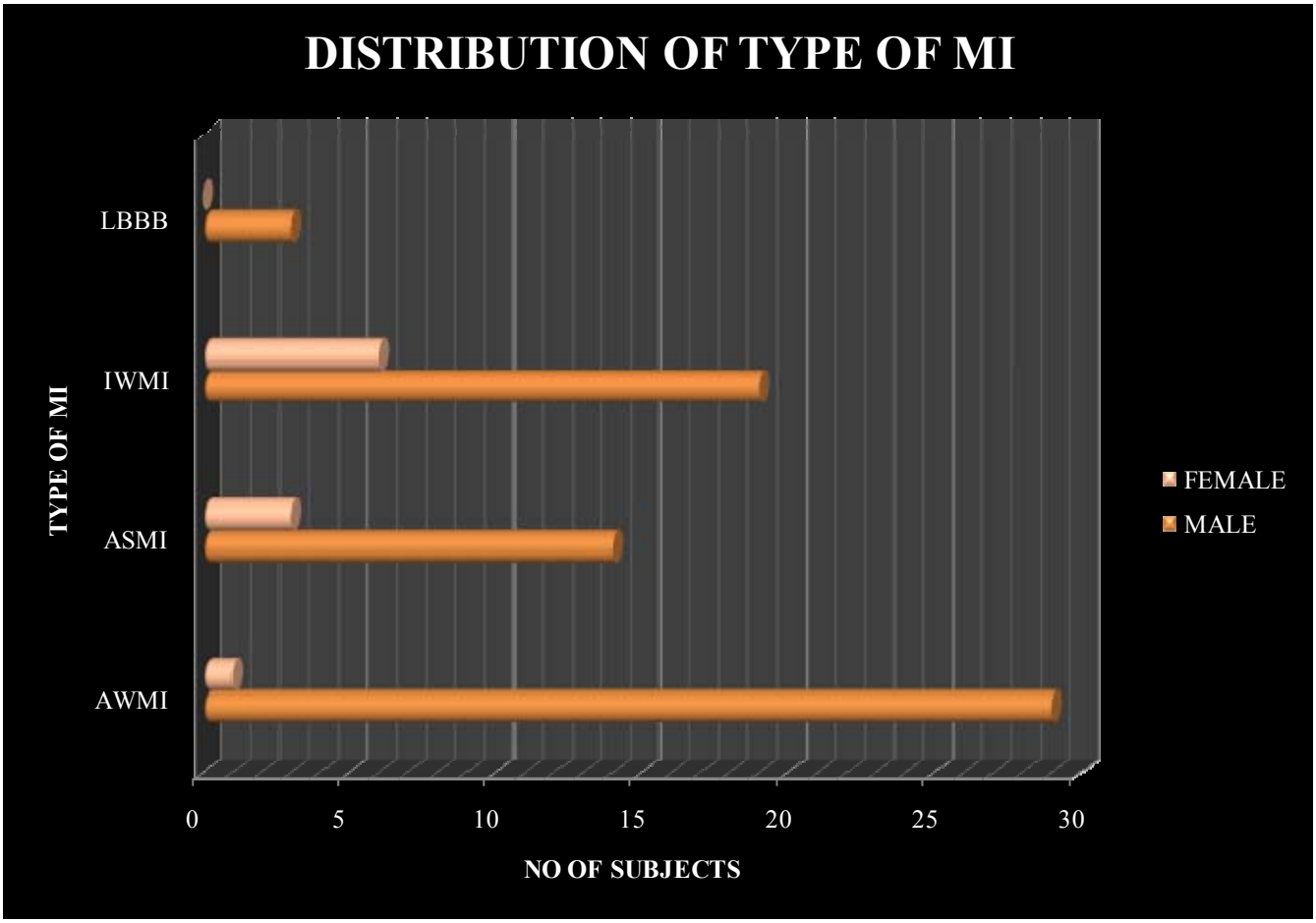


FIGURE 9: Anterior wall MI was the commonest encountered type in the studied population.

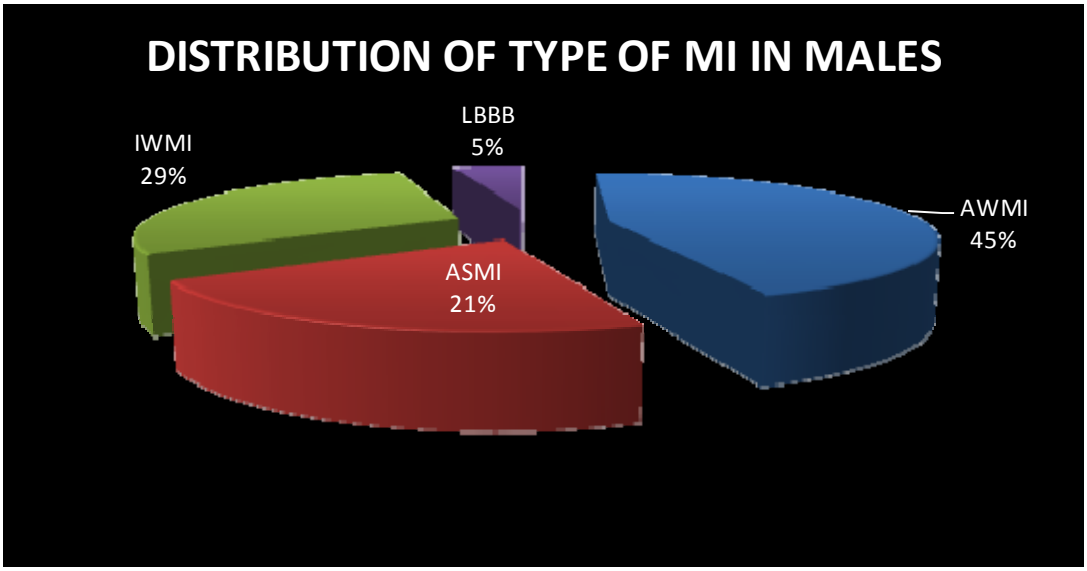


FIGURE 10: Majority of the males suffered anterior wall infarction.

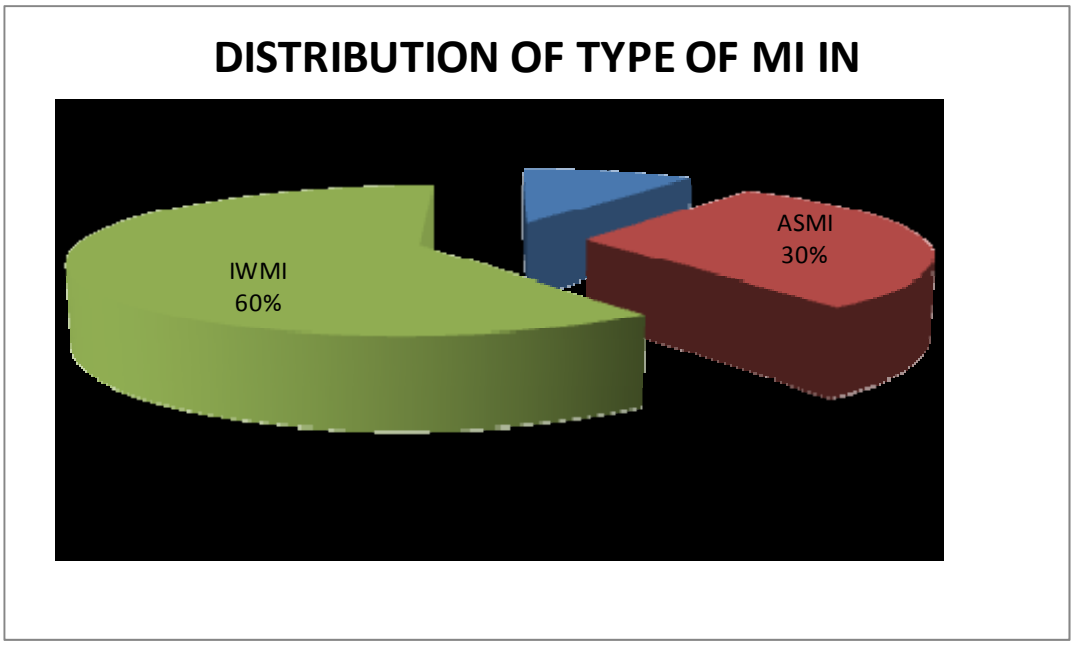


FIGURE 11: Inferior wall MI was the commonest presentation among females.

DISTRIBUTION OF TYPES OF MYOCARDIAL INFARCTION IN DIFFERENT URIC ACID QUARTILES(TABLE 16)

TYPE OF MI	SERUM URIC ACID IN mg/dl			
	3.1- 5.0	**5.1 – 7.0**	**7.1 – 9.0**	**>9.0**
AWMI	0	10	17	3
ASMI	3	12	2	1
IWMI	11	10	5	0
LBBB	0	0	2	1

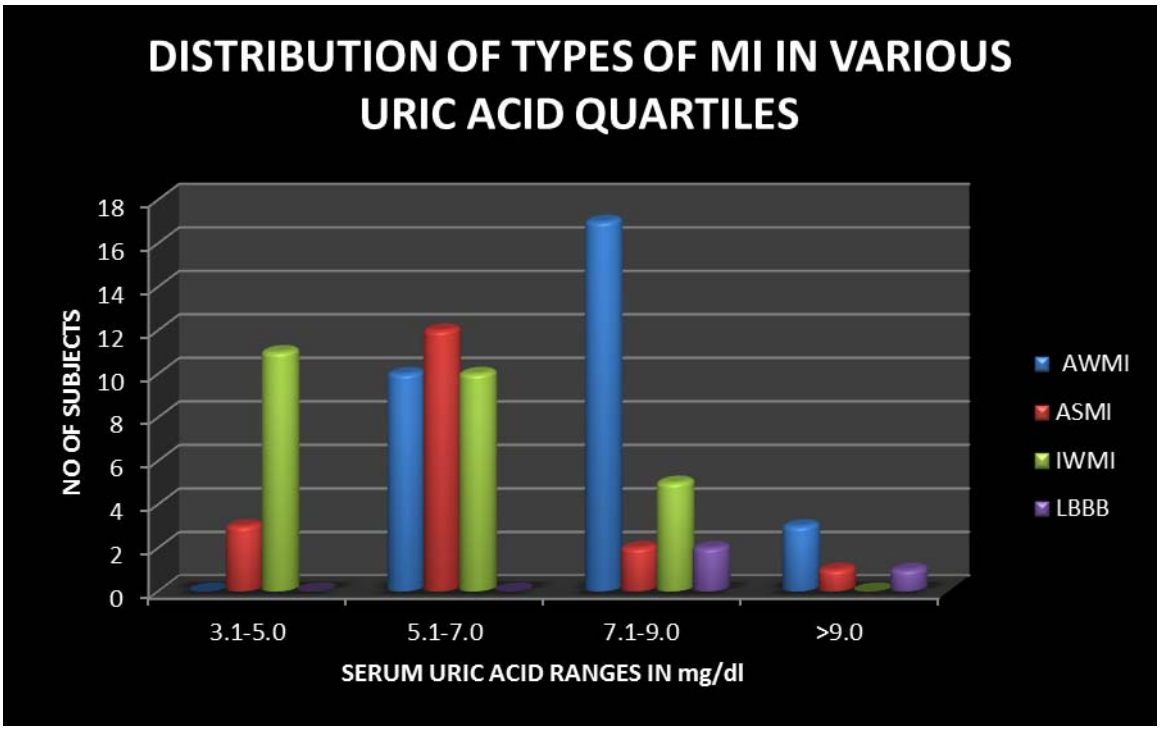


FIGURE 12

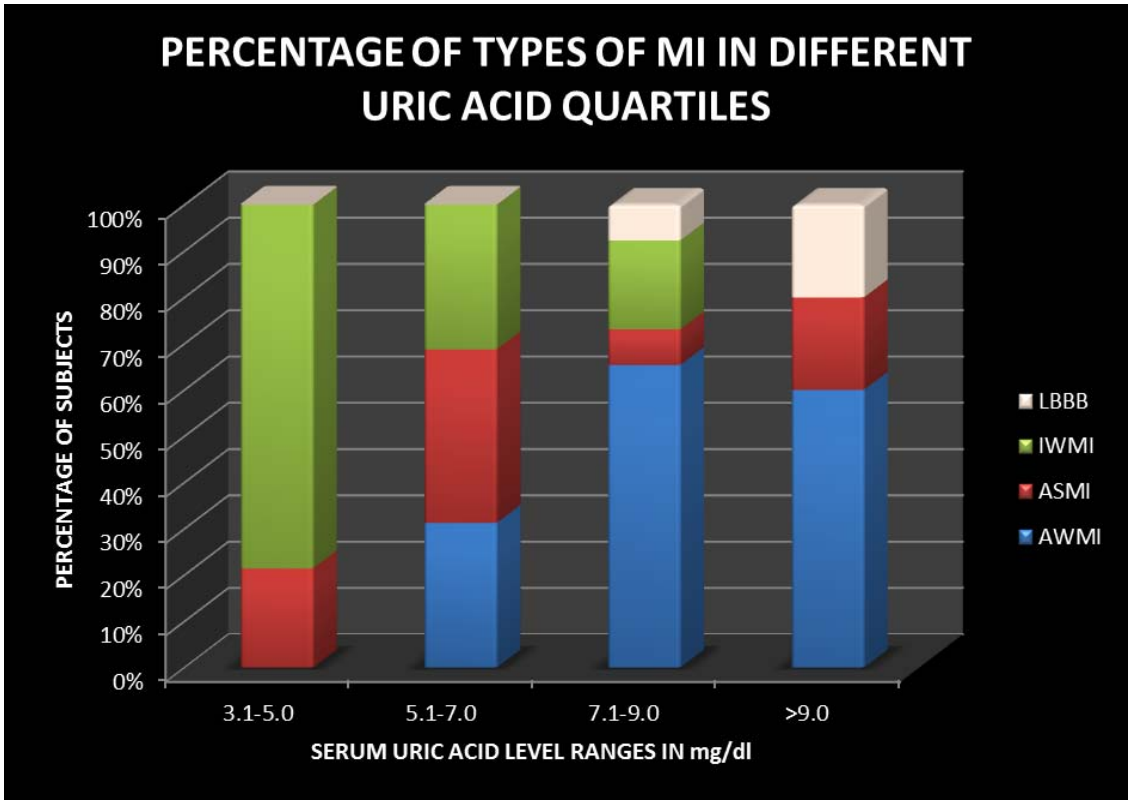


FIGURE 13: Anterior wall MI and LBBB pattern were associated with higher uric acid quartiles while inferior wall MI was associated with lower uric acid quartiles.

Table-17. **Association between Serum uric acid and Type of STEMI.**

Type	Acute STEMI Sr uric acid			χ^2	df	Sig.
	Hyper	Non Hyper	Total			
AS	7	10	17	23.247	1	P<0.01
AW	22	8	30			
IW	2	13	15			
IWPW	2	3	5			
IWRVPW	3	0	3			
IWRV	0	1	1			
LBBB	3	0	3			
LWRW	0	1	1			
Total	39	36	75			

Table 17 shows the relation between type of STEMI with Uric acid. Anterior wall MI was associated with Hyperuricemia and Inferior wall MI was associated with Non Hyperuricemia (P<0.01).

DISTRIBUTION OF KILLIP CLASS AMONG STUDY POPULATION

(TABLE 18)

KILLIP	I	II	III	IV
MALE	35	17	7	6
FEMALE	8	1	1	0
TOTAL	43	16	8	6

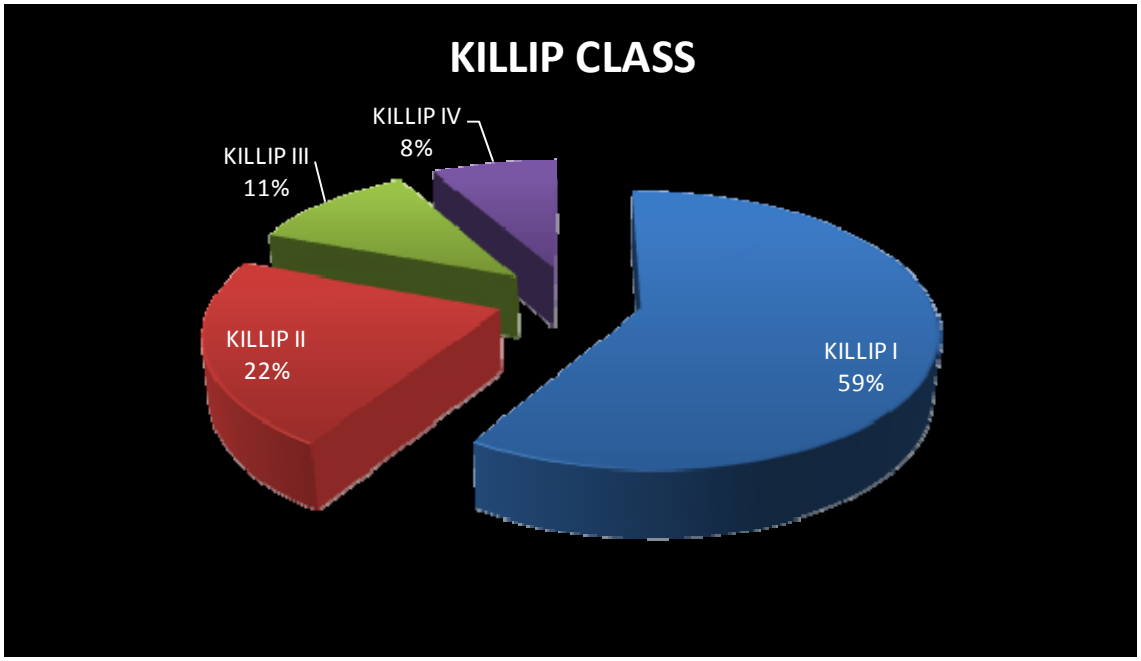


FIGURE 14: Majority of the subjects were in Killip class I .

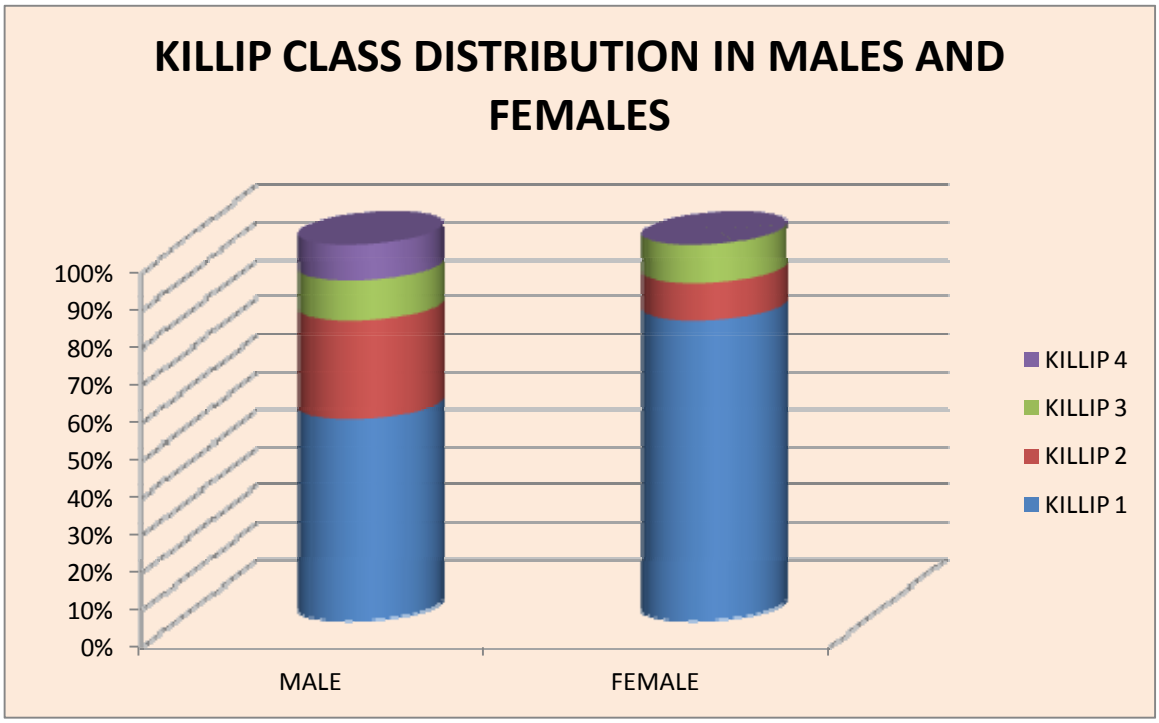


FIGURE 15: 80% of females presented with Killip class 1. Higher Killip classes occurred commonly in men.

COMPARISON OF URIC ACID LEVELS WITH KILLIP CLASS
(TABLE 19)

KILLIP CLASS	SERUM URIC ACID IN mg/dl			
	3.1-5.0	**5.1-7.0**	**7.1-9.0**	**>9.0**
KILLIP I	13	25	4	1
KILLIP II	0	5	12	1
KILLIP III	0	0	5	2
KILLIP IV	0	0	5	1

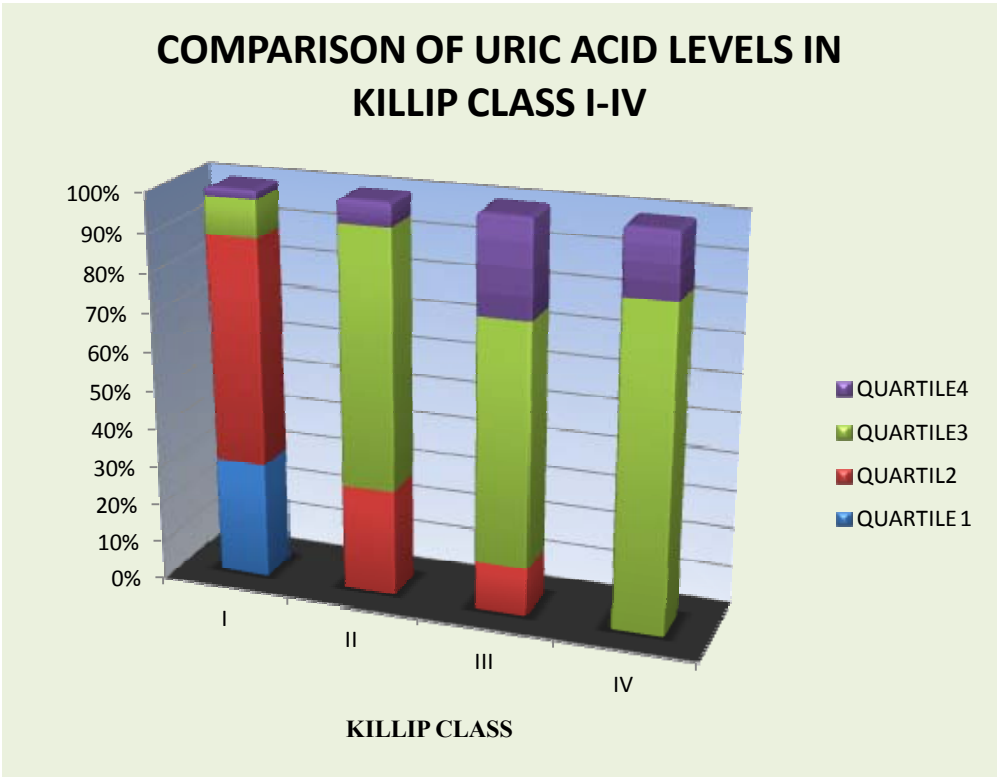


FIGURE:16 : Higher Killip Classes were associated with higher uric acid levels

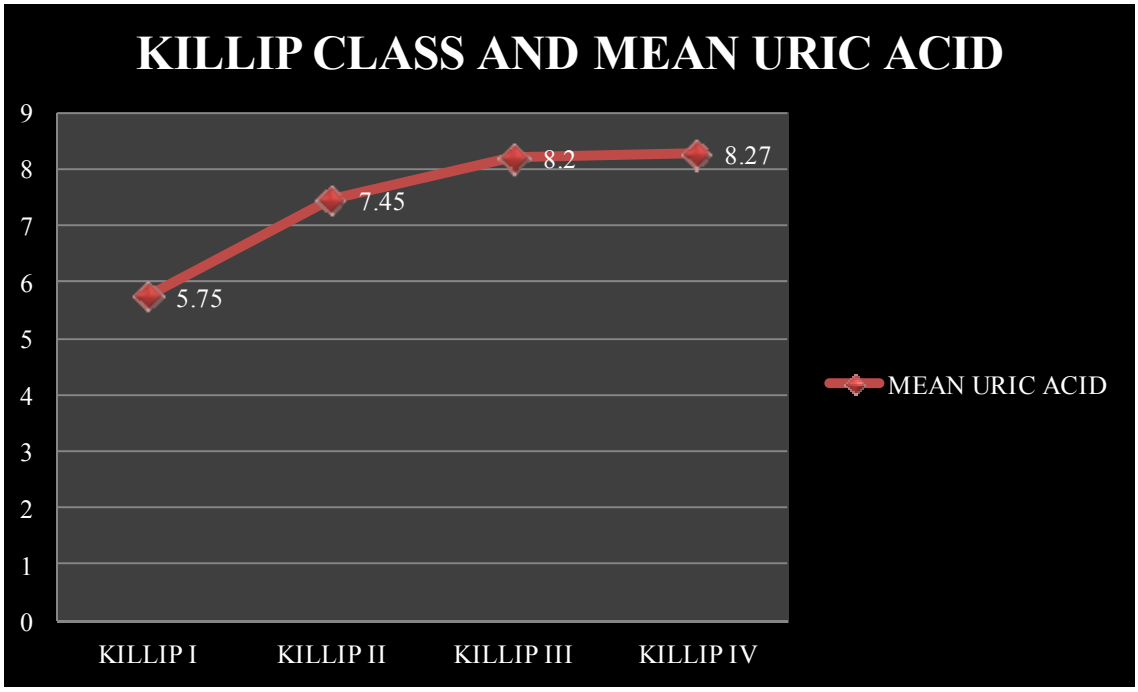


FIGURE:17 : Mean uric acid levels were higher in Killip class III and IV

Table-20**. Association between Sr uric acid and Killip class.**

Killip class	Acute STEMI Sr uric acid			χ^2	Df	Sig.
	Hyper	Non Hyper	Total			
I	10	33	43	33.625	3	P<0.001
II	16	2	18			
III	7	1	8			
IV	6	0	6			
Total	39	36	75			

Table 20 shows the association between serum uric acid and Killip class.

Killip class III and IV were strongly associated with Hyperuricemia. (P<0.001).

CORRELATION BETWEEN TIMI SCORE AND URIC ACID LEVEL

(TABLE 21)

MEAN SUA IN mg/dl	TIMI RISK SCORE										
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**12**
IN MEN	4.4	4.75	5.62	6.7	7.11	7.72	7.2	8	8.15	8.7	8.8
IN WOMEN	4.2	4.7	5.85	6.2	6.2	-	-	6.9	-	-	-

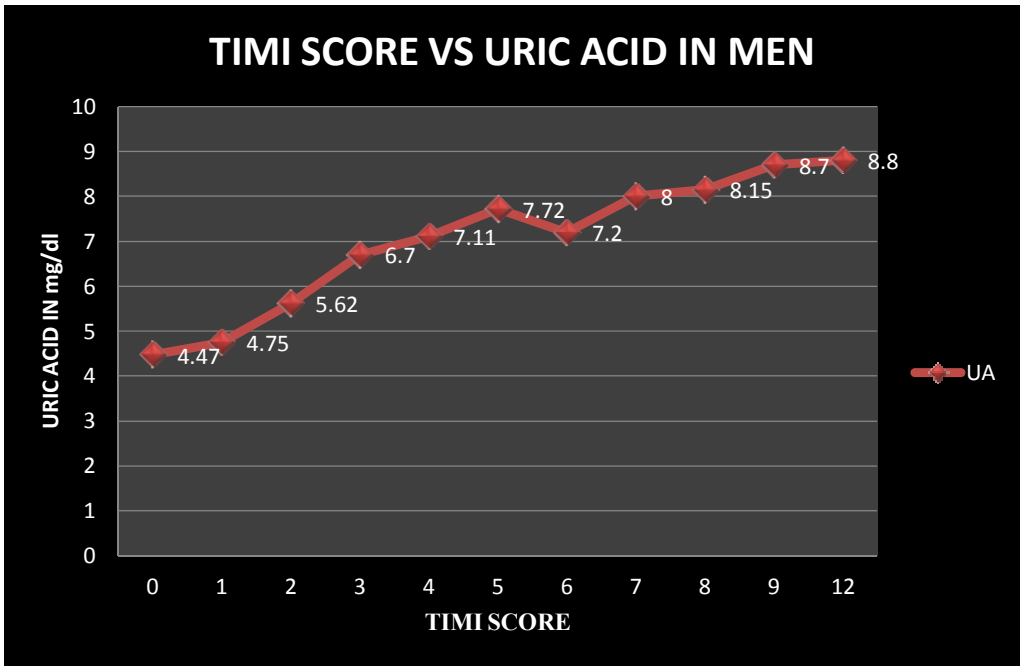


FIGURE 18: Uric acid levels increased with age in males.

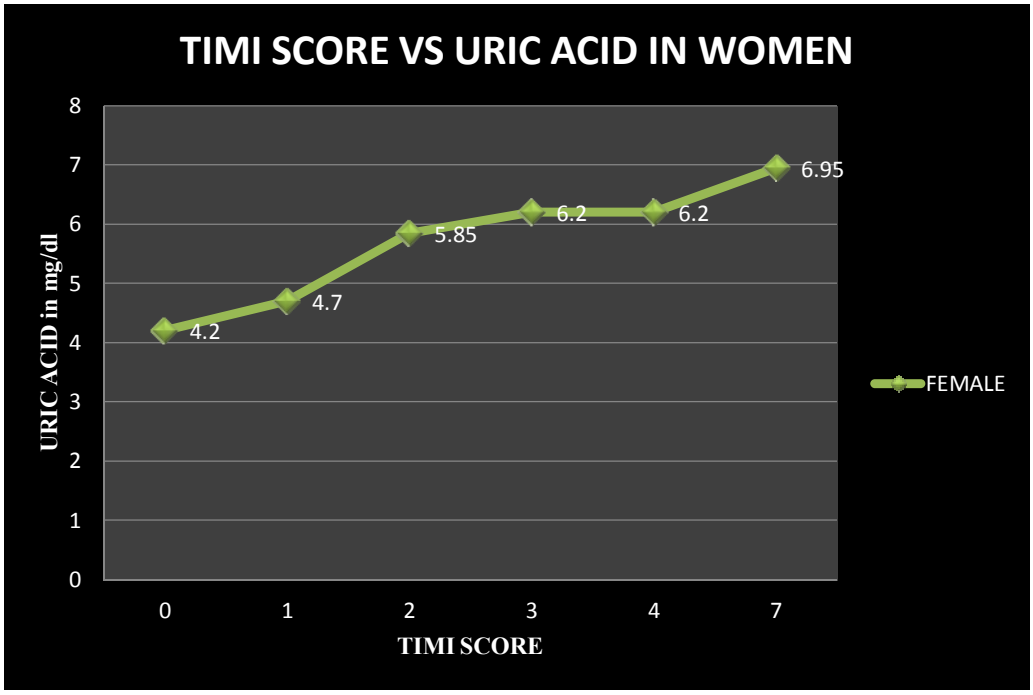


FIGURE 19: Uric acid levels increased with increase in TIMI risk score in both male and female populations.

Comparison of Hyperuricemia and Non-Hyperuricemia cases based on TIMI score (Table 22)

Variables	Hyperuricemia		Non-Hyperuricemia		Difference B/W H & NH	't'	df	Sig.
	Mean	SD	Mean	SD				
TIMI	6.5	2.1	1.7	1.4	4.8	11.610	73	P<0.001

TIMI score differed significantly between the two groups(P<0.001).

DISTRIBUTION OF URIC ACID LEVELS IN DIABETICS AND NON-DIABETICS (TABLE 23)

GLYCEMIC STATUS	SERUM URIC ACID IN mg/dl			
	QUARTILE1 3.1-5.0	QUARTILE2 5.1-7.0	QUARTILE3 7.1-9.0	QUARTILE4 >9.0
DIABETICS	3	10	14	2
NON DIABETICS	10	21	12	2

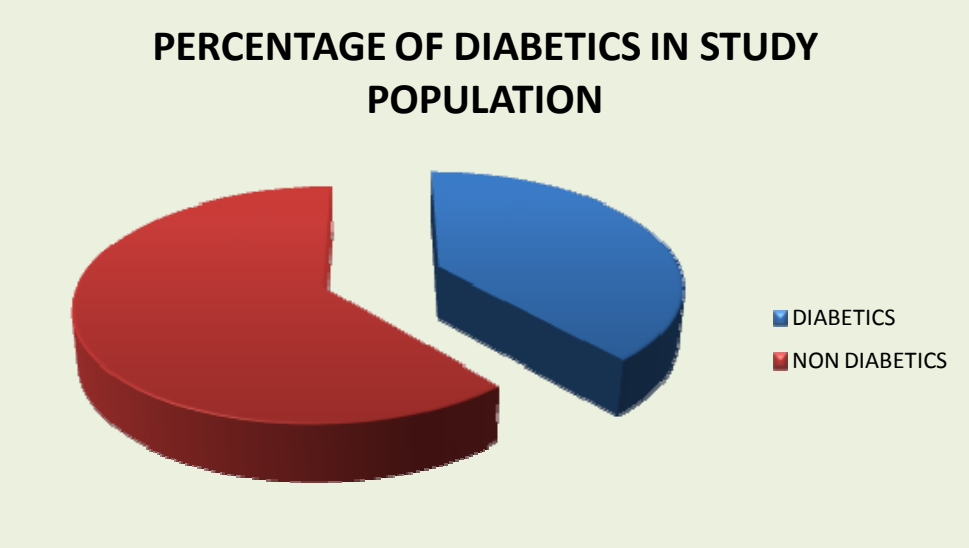


FIGURE 20: 39% of the total population had Diabetes

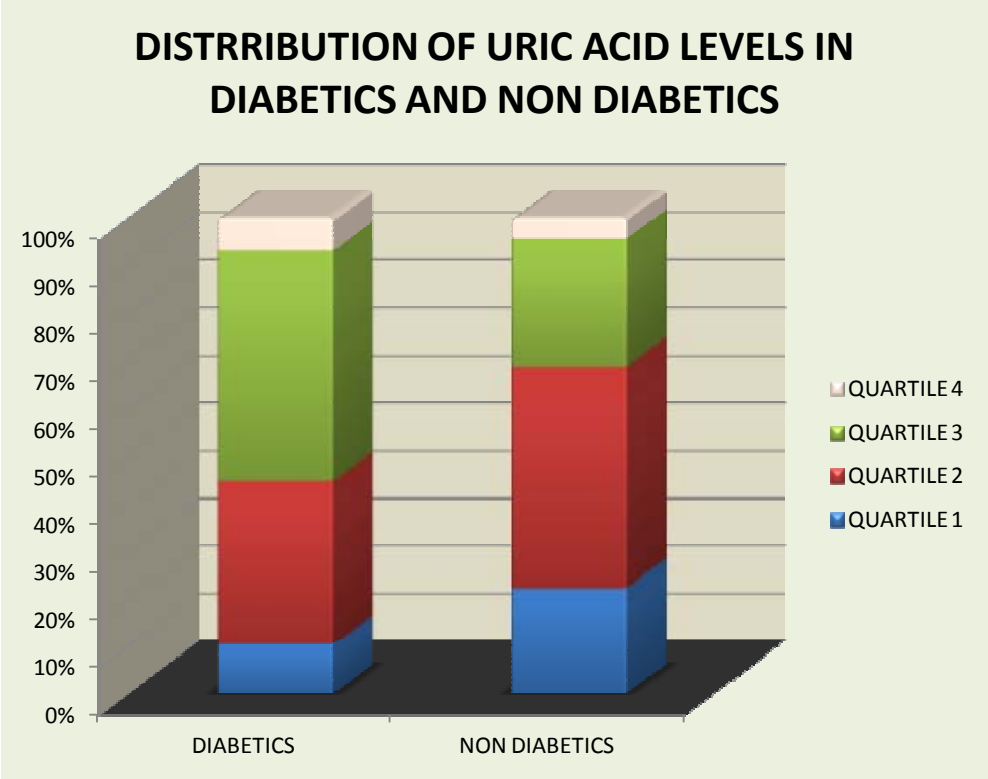


FIGURE 21: Diabetics had higher uric acid levels when compared to non diabetics.

COMPARISON OF URIC ACID LEVELS IN NORMOTENSIVES AND HYPERTENSIVES(TABLE 25)

	SERUM URIC ACID (in mg/dl)			
	QUARTILE1 3.1-5.0	**QUARTILE2 5.1-7.0**	**QUARTILE3 7.1-9.0**	**QUARTILE 4 >9.0**
NORMOTENSIVES	12	23	11	2
HYPERTENSIVES	1	8	15	3

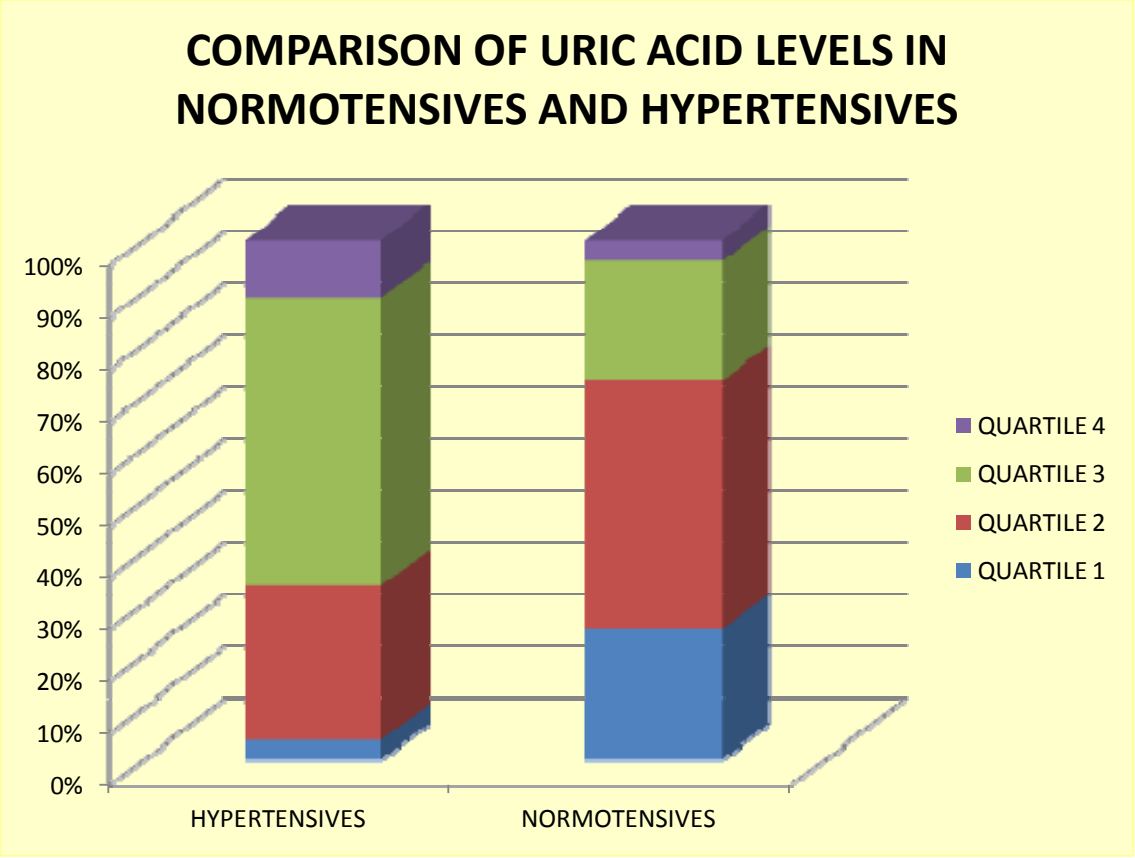


FIGURE 22: The presence of hypertension was associated with higher uric acid levels.

Table-26. **Association of Serum uric acid with Diabetes and Hypertension**

Risk Factors	Acute STEMI Sr uric acid			χ^2	df	Sig.
	Hyper	Non Hyper	Total			
Diabetic	11	8	19	15.562	3	P<0.001
Hyperten	11	5	16			
DM+HT	9	1	10			
NIL	8	22	30			
Total	39	36	75			

The Risk Factors such as Diabetes, Hypertension and DM+HT were associated with Hyperuricemia and the absence of these risk factors was associated with Non- Hyperuricemia (P<0.001).

COMPARISON OF URIC ACID IN SMOKERS AND NON SMOKERS

(TABLE 27)

	SERUM URIC ACID IN mg/dl			
	QUARTILE1 3.1-5.0	**QUARTILE2 5.1-7.0**	**QUARTILE3 7.1-9.0**	**QUARTILE4 >9.0**
SMOKERS	6	14	12	5
NON SMOKERS	6	8	13	0

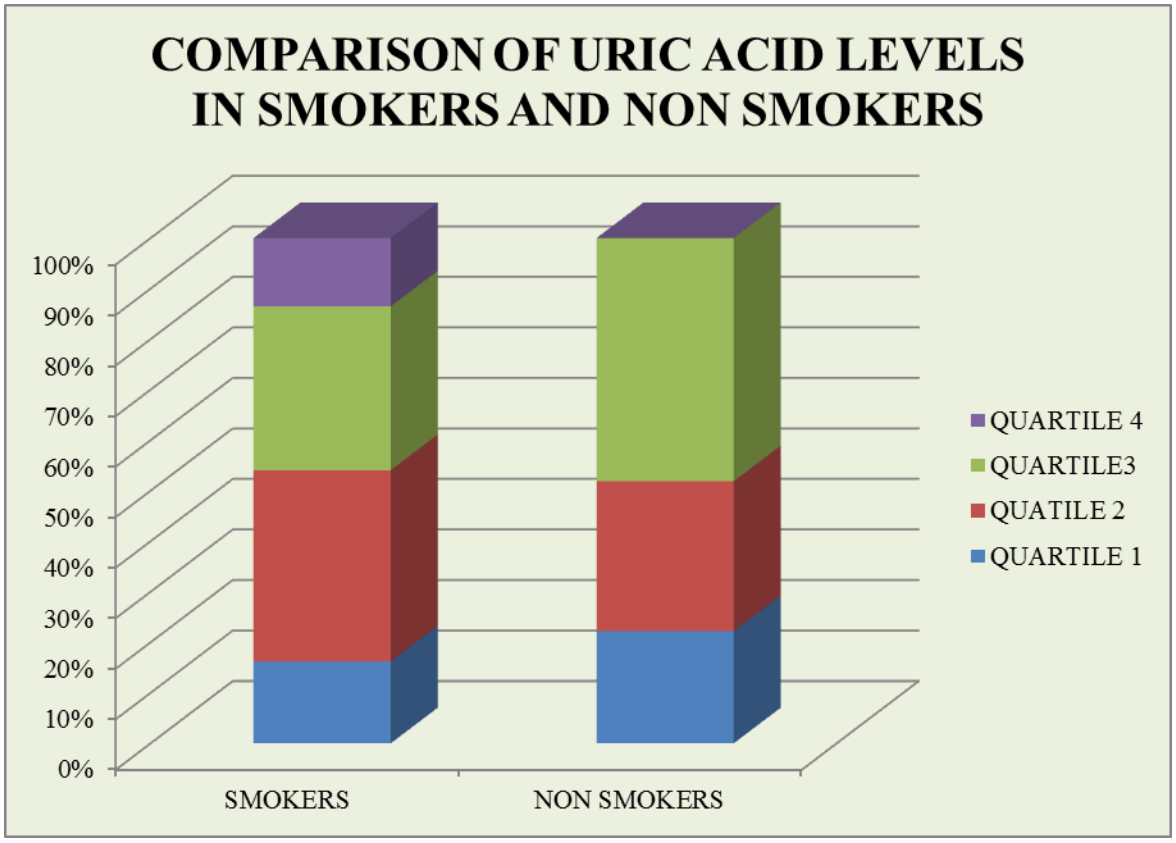


FIGURE 23: The distribution of uric acid levels were similar in smokers and non smokers.

Table-28. **Association between serum uric acid with smoking habit**

Smoking	**Acute STEMI Sr uric acid**			**χ^2**	**df**	**Sig.**
	Hyper	**Non Hyper**	**Total**			
Yes	18	19	37	0.329	1	P>0.05
No	21	17	38			
Total	39	36	75			

Table 28 shows the association between serum uric acid with smoking . Smoking did not have any significant association with Sr. Uric Acid (P>0.05).

CORRELATION OF MEAN URIC ACID WITH NUMBER OF RISK FACTORS (TABLE 29)

MEAN URIC ACID IN mg/dl	NO OF RISK FACTORS				
	0	1	2	3	4
IN MALES	5.2	6.42	7.11	8.2	8.75
IN FEMALES	6.08	6.15	5.5	5.2	-

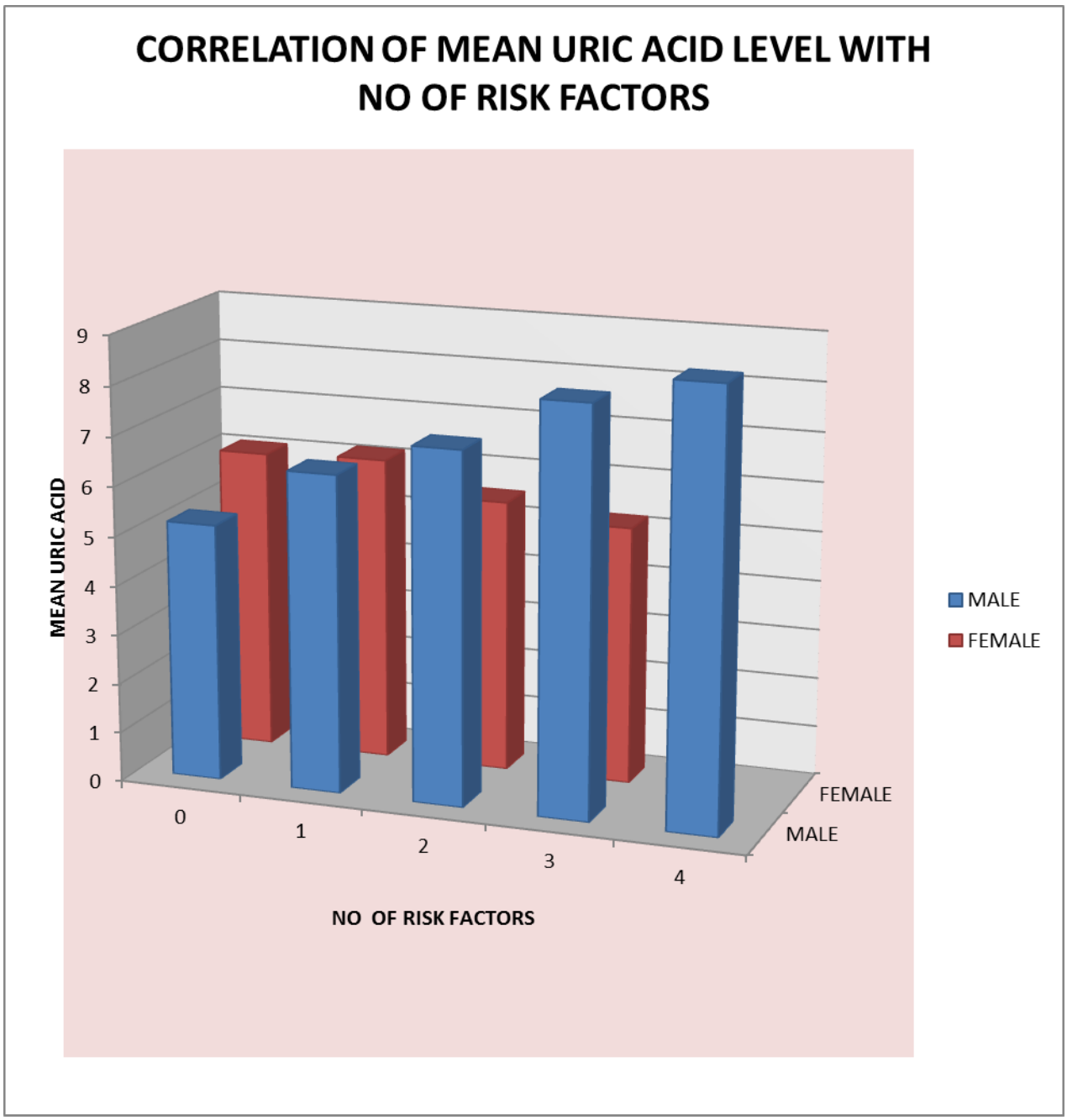


FIGURE 24: The presence of diabetes, hypertension, smoking, family history of CAD was compared with uric acid level. Uric acid level increases with number of risk factors. This positive correlation is not seen in female population.

COMPARISON OF TRIGLYCERIDE LEVEL WITH URIC ACID

(TABLE 30)

TRIGLYCERIDE in mg/dl	URIC ACID LEVELS IN mg/dl			
	3.1-5.0	5.1-7.0	7.1-9.0	>9.0
50-150	11	15	9	0
151-300	2	14	14	5
>300	0	2	3	0

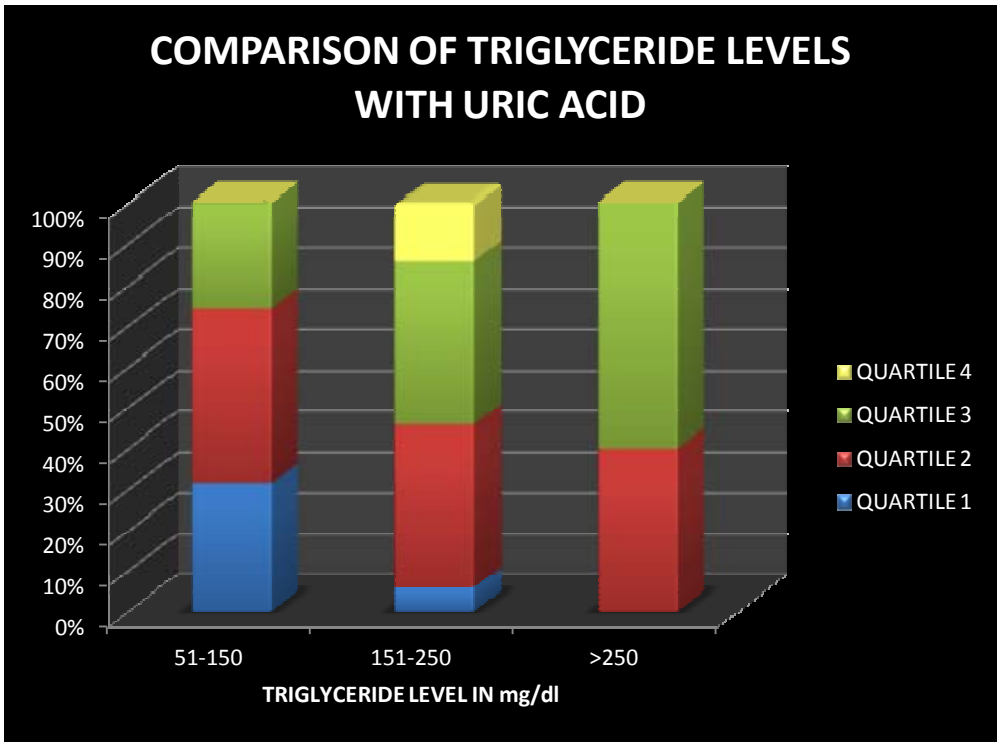


FIGURE 25: Uric acid increased with increase in triglyceride level

Table 31. **Comparison of Hyperuricemia and Non-Hyperuricemia cases based on Triglyceride levels**

Variables	Hyperuricemia		Non-Hyperuricemia		Difference B/W H & NH	't'	df	Sig.
	Mean	SD	Mean	SD				
TGL	171.1	46.9	144.4	36.2	26.7	2.741	73	P<0.01

Triglyceride levels differed significantly between the two groups(P<0.01).

COMPARISON OF URIC ACID LEVEL WITH SERUM TOTAL CHOLESTEROL(TABLE 32)

TOTAL CHOLESTEROL	SERUM URIC ACID IN mg/dl			
	3.1-5.0 QUARTILE1	5.1-7.0 QUARTILE2	7.1-9.0 QUARTILE3	>9.0 QUARTILE4
<100 mg/dl	1	0	0	1
101-200 mg/dl	12	23	19	1
201-300 mg/dl	0	7	6	3
>300 mg/dl	0	1	1	0

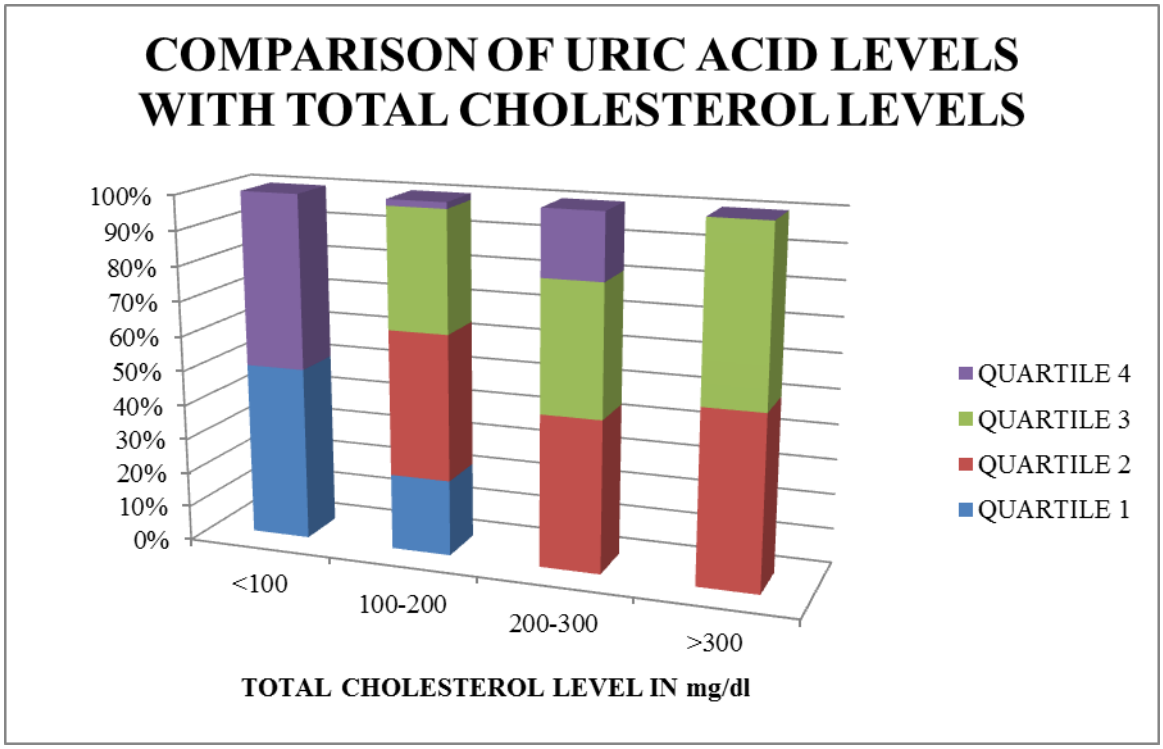


FIGURE 26: There was no significant association between serum total cholesterol levels and uric acid.

COMPARISON OF NORMOURICEMIC AND HYPERURICEMIC GROUPS BASED ON TOTAL CHOLESTEROL LEVELS

(TABLE 33)

Variables	Hyperuricemia		Non-Hyperuricemia		Difference B/W H & NH	't'	df	Sig.
	Mean	SD	Mean	SD				
Cholesterol	193.4	46.0	174.59	38.2	18.5	1.877	73	P>0.05

There was no significant difference in the total cholesterol levels between the two groups.

COMPARISON OF URIC ACID LEVELS WITH BODY MASS INDEX

(TABLE 34)

BMI	URIC ACID IN mg/dL			
	3.1-5.0 QUARTILE 1	5.1-7.0 QUARTILE2	7.1-9.0 QUARTILE3	>9 QUARTILE4
20.1-25	13	19	19	3
25.1-30	0	10	5	2
>30	0	2	2	0

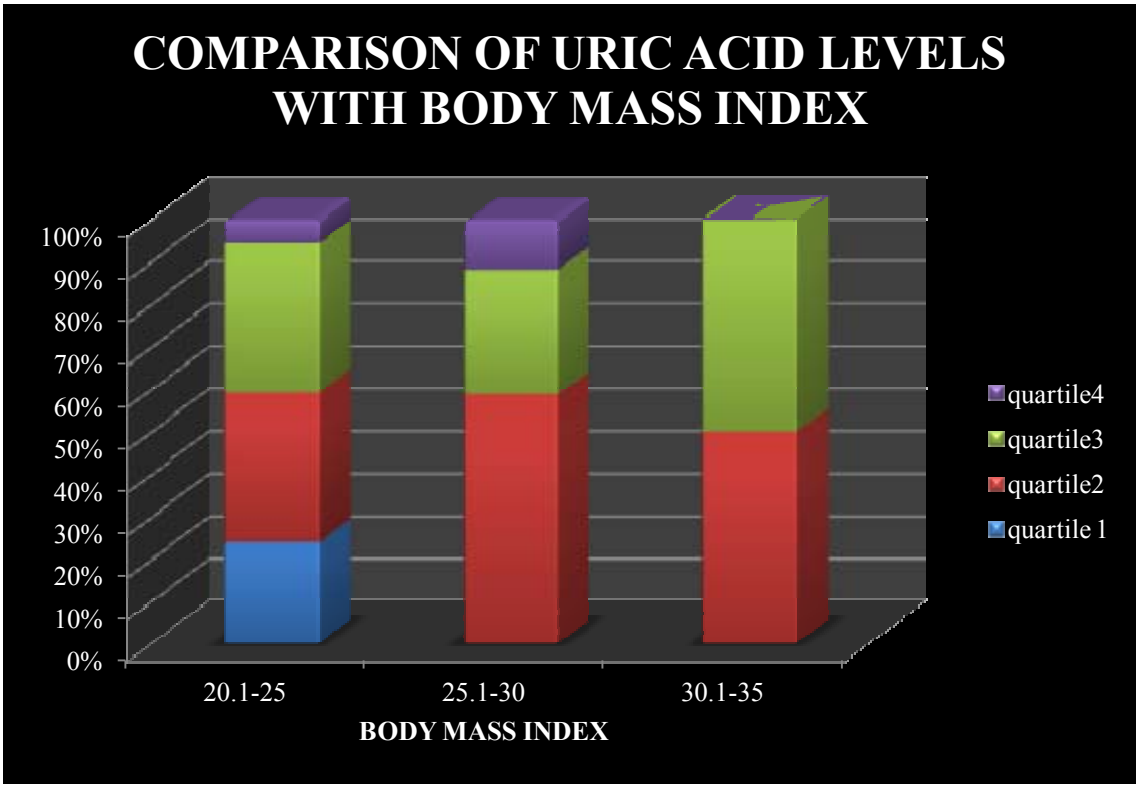


FIGURE 27: there was no significant association between uric acid levels and BMI.

Table 35**. Comparison of Hyperuricemia and Non-Hyperuricemia cases according to their age, window period and related Bio- chemical variables.**

Variables	Hyperuricemia		Non-Hyperuricemia		Difference B/W H & NH	't'	df	Sig.
	Mean	SD	Mean	SD				
Age (years)	64.2	7.2	50.8	10.9	13.4	6.297	73	P<0.001
Window (Days)	4.2	1.7	3.9	1.5	0.3	0.707	73	P>0.05
Pulse rate	88.4	24.2	81.4	11.2	7.0	1.582	73	P>0.05
Cholesterol	193.4	46.0	174.59	38.2	18.5	1.877	73	P>0.05
TGL	171.1	46.9	144.4	36.2	26.7	2.741	73	P<0.01
BMI	24.9	2.5	24.6	2.9	0.3	0.485	73	P>0.05
SBP	124.9	34.3	131.1	15.8	6.2	0.947	73	P>0.05
DBP	76.9	24.4	79.2	9.4	2.3	0.517	73	P>0.05
TIMI	6.5	2.1	1.7	1.4	4.8	11.610	73	P<0.001

Uric acid levels showed a positive correlation with age, Triglyceride levels, Killip class and TIMI risk scores. It also showed a significant association with Diabtes and Hypertension.

COMPARISON OF EJECTION FRACTION WITH URIC ACID LEVELS (TABLE 36)

EJECTION FRACTION	SERUM URIC ACID IN mg%			
	3.1-5.0	**5.1-7.0**	**7.1-9.0**	**>9.0**
25.1-30.0	0	0	3	2
30.1-35.0	0	0	4	1
35.1-40.0	0	12	11	1
40.1-45.0	8	14	4	0
45.1-50.0	4	2	3	0
>50.0	1	2	0	0

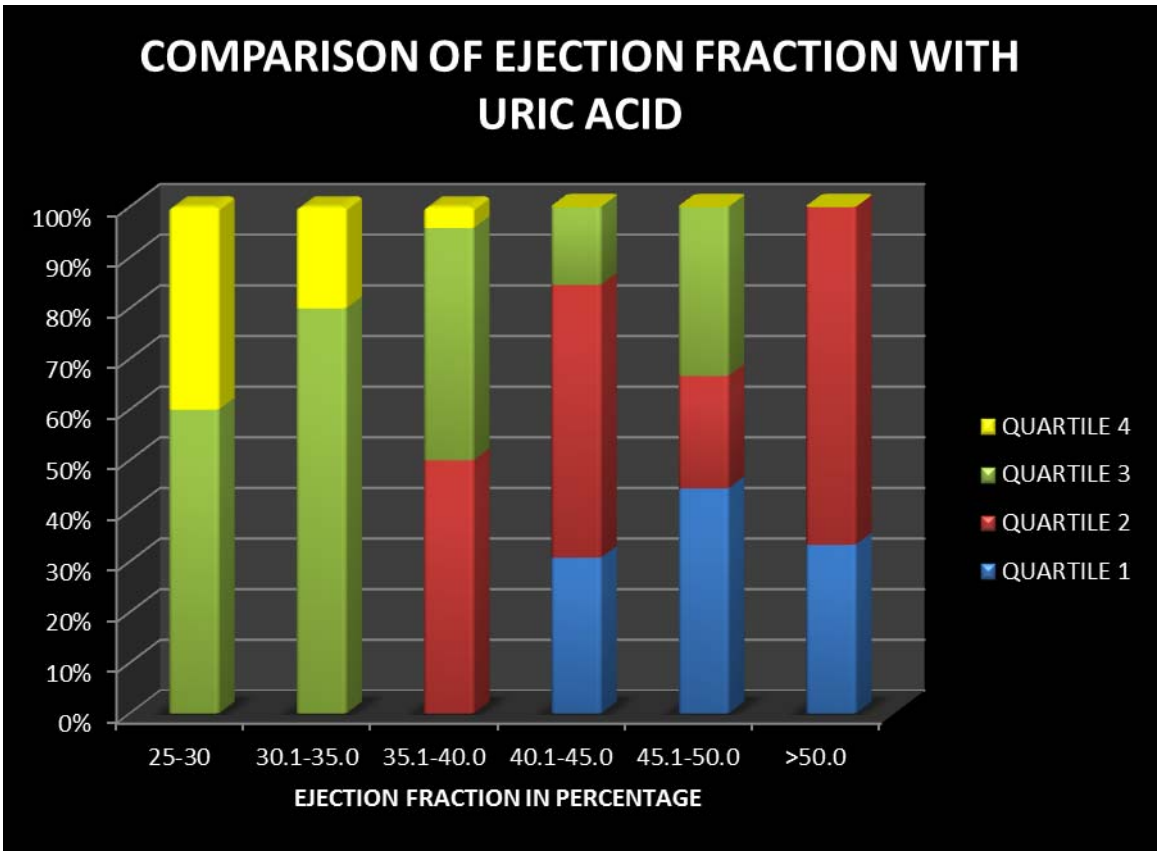


FIGURE 28: Lower ejection fraction was associated with higher uric acid quartiles.

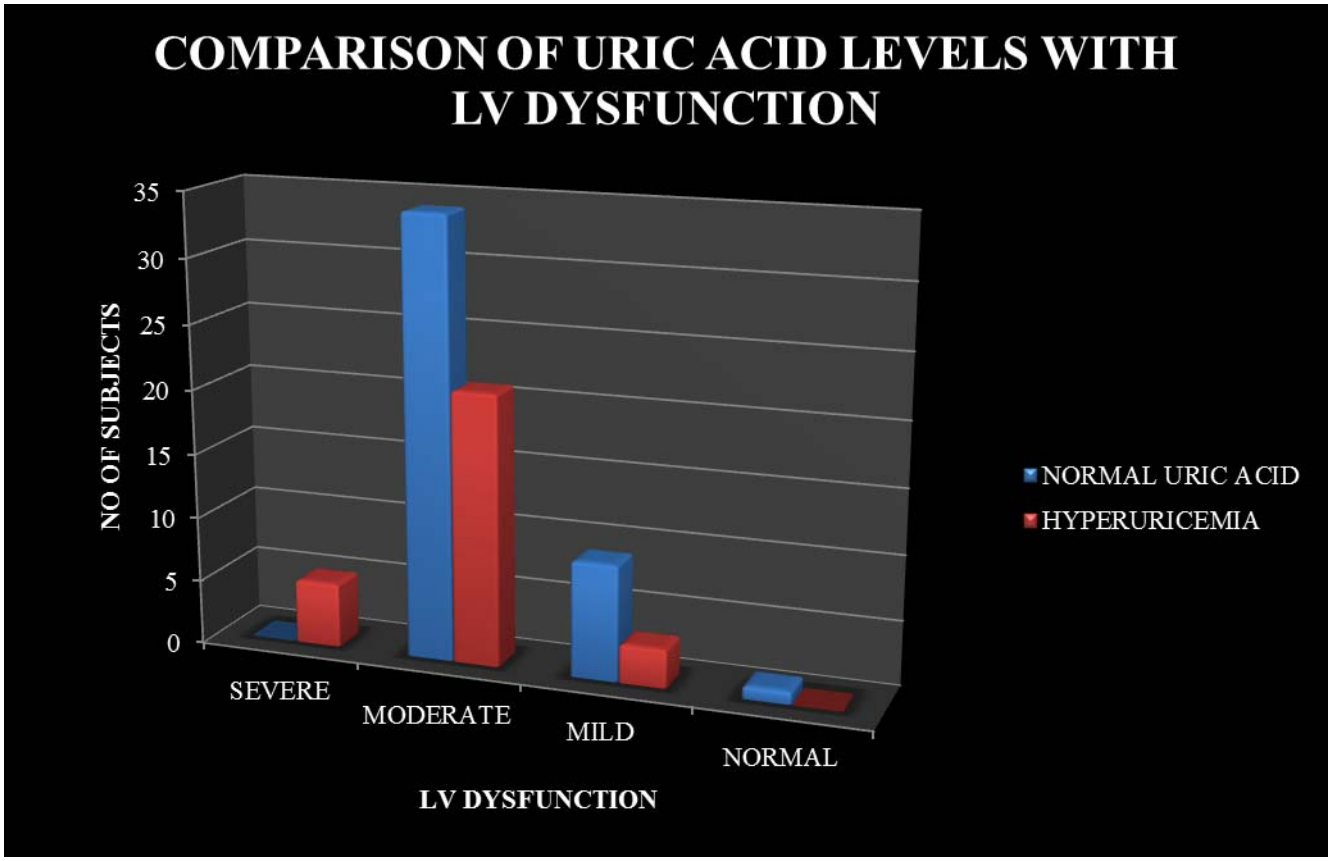
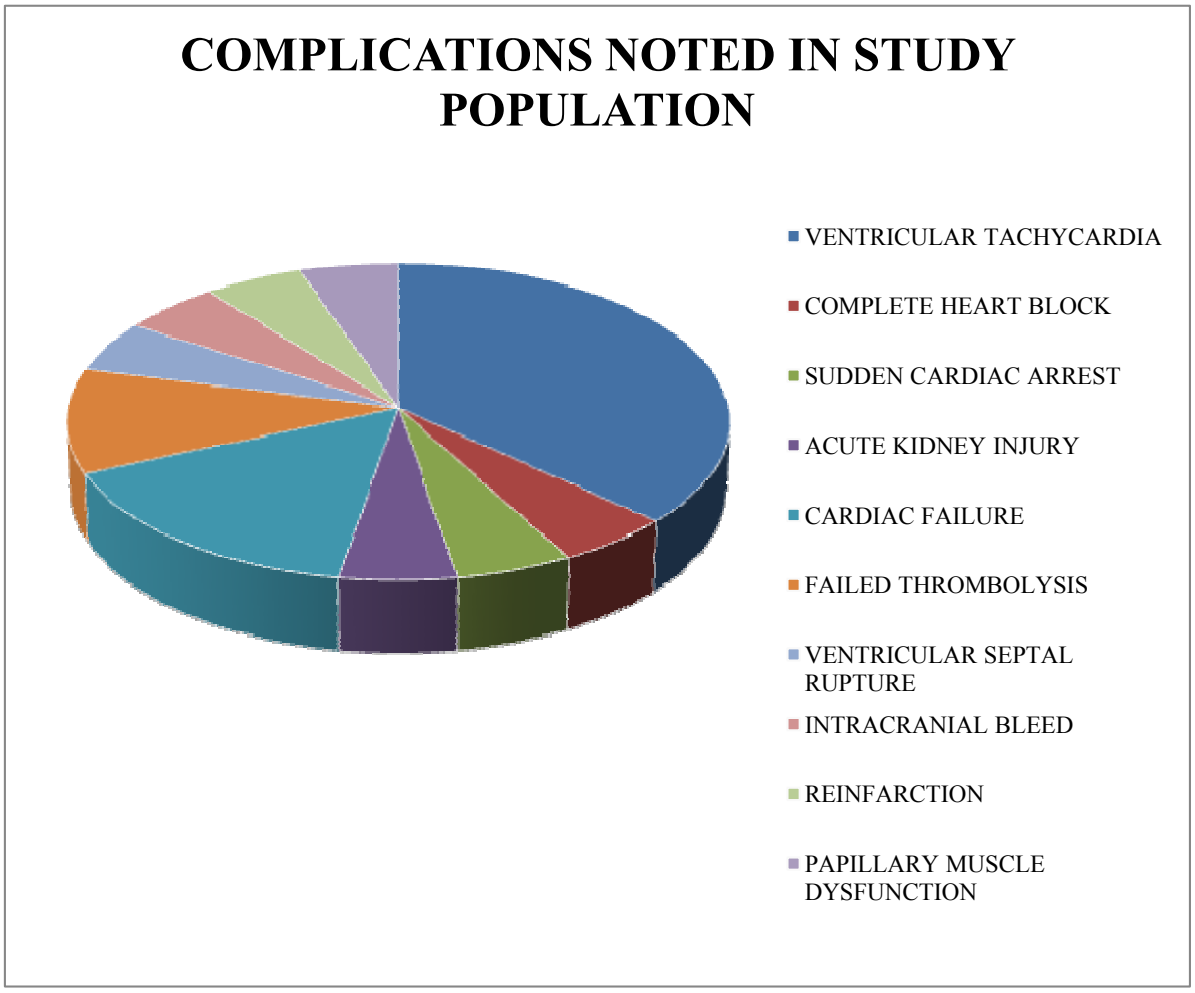


FIGURE 29: All patients with severe LV dysfunction had uric acid>7 mg/dl while only 25% of the subjects with mild LV dysfunction had hyperuricemia

All patients with LV ejection fraction< 30% had sustained anterior wall MI. among the subjects with moderate and severe LV dysfunction, 45% of them had anterior wall MI. All 3 patients with LBBB had moderate LV dysfunction. 72% of the subjects with mild LV dysfunction had Inferior wall MI.

None of the patients with normal uric acid levels had severe LV dysfunction whereas 16.7% of patients with hyperuricemia suffered severe LV dysfunction.

FIGURE 30



Among the study group, 21 subjects developed some sort of complication. The mortality among those who had complications during hospital stay was 23%. 3.3% of the study population experienced arrhythmias during hospital stay. The most common among them was ventricular tachycardia. The majority of the arrhythmias occurred on the day of admission. 20% of those who sustained arrhythmias died. Two patients had ventricular septal rupture and both went in for severe LV dysfunction and died. Totally 18% of the patients went in for cardiac failure. The short term mortality among them was 23%.

COMPARISON OF INCIDENCE OF COMPLICATIONS IN HYPERURICEMIA GROUP WITH NORMAL URIC ACID GROUP

(TABLE 37)

Complications	Acute STEMI Sr uric acid			χ^2	df	Sig.
	Hyper	Non Hyper	Total			
A	2	2	3	23.496	12	P<0.05
AKI,F	1	0	1			
CHB	1	0	1			
CHB,VSR	1	0	1			
VT	7	0	7			
FT,F	1	0	1			
FT,VT,F	1	0	1			
ICH	1	0	1			
RS	1	0	1			
VSR	1	0	1			
PMD	1	0	1			
F	3	0	3			
Nil	1	0	1			
Total	21	34	53			

This table shows the significant association of hyperuricemia with complications in STEMI. (A- Sudden cardiac arrest, F- Failure, AKI –Acute Kidney Injury, VSR- Ventricular septal rupture, PMD- Papillary muscle dysfunction, FT- Failed Thrombolysis, R-Reinfarction, S-Shock, ICH Intracranial hemorrhage, VT-Ventricular Tachycardia, CHB-Complete Heart Block)

When the uric acid levels on day 1 and day 3 were compared, 21 patients had raised uric acid levels on day 3. 71% of subjects with adverse cardiac events presented with higher uric acid levels on day 3 whereas only 11% of patients who were uneventful after thrombolysis presented with higher levels on day 3.

COMPARISON OF MORTALITY IN NORMAL URIC ACID AND HYPERURICEMIA GROUPS(TABLE 38)

	NORMAL URIC ACID	HYPERURICEMIA GROUP
TOTAL SUBJECTS	44	31
NO OF DEATHS	1	5

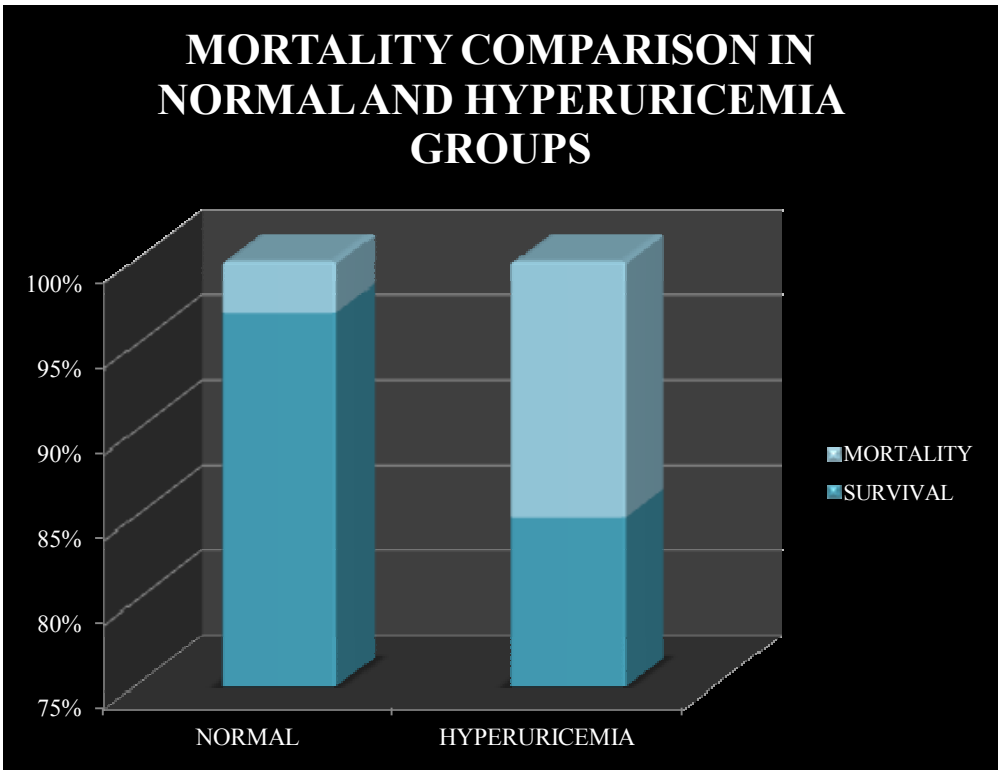


FIGURE 31:Mortality was higher in patients with hyperuricemia (12.8%) when compared to subjects with normal uric acid levels.(2.7%)

CORRELATION OF URIC ACID LEVELS WITH MORTALITY

(TABLE 39)

	SERUM URIC ACID IN mg/dl			
	3.1-5.0	**5.1-7.0**	**7.1-9.0**	**>9.0**
TOTAL SUBJECTS	13	31	26	5
NO OF DEATHS	0	1	2	3

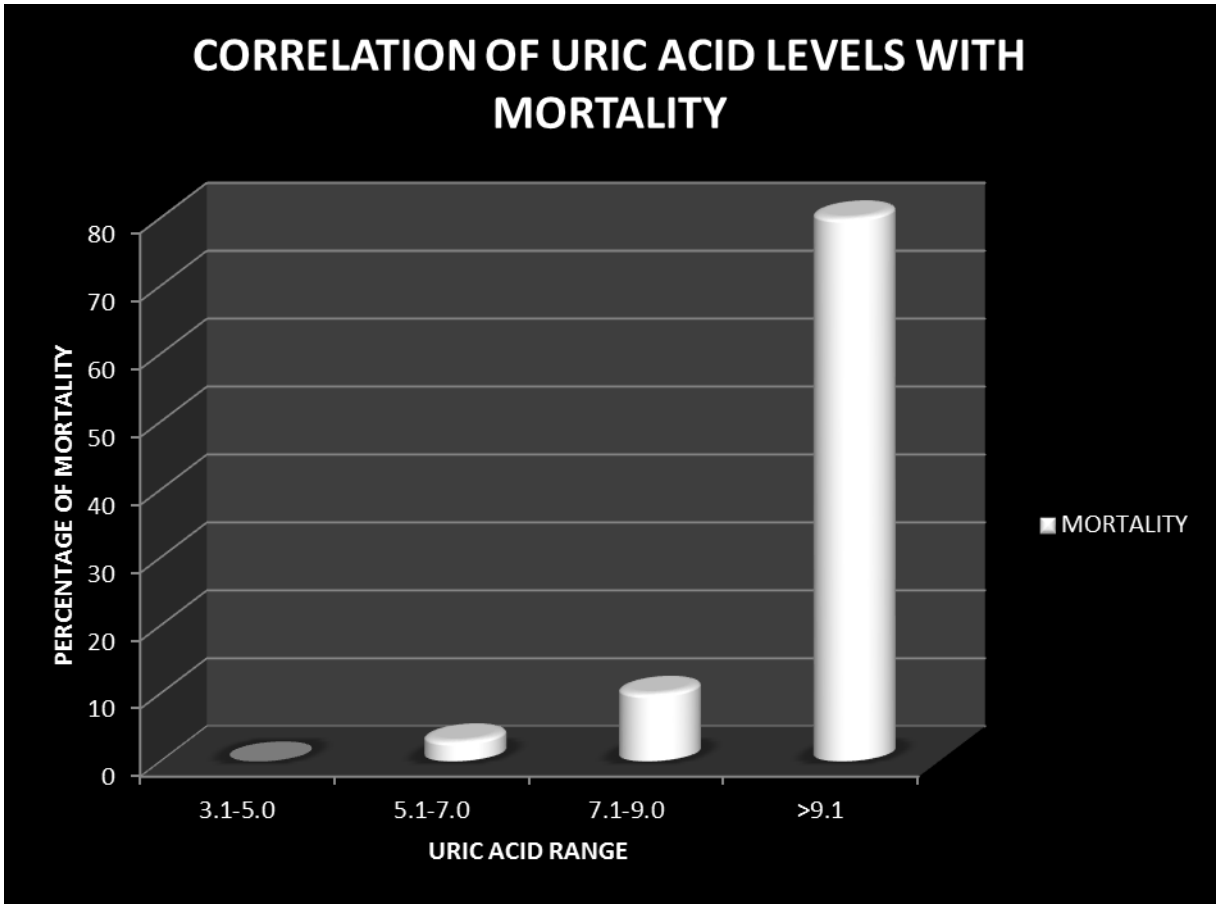


FIGURE 32: Patients with uric acid level >9 mg/dl had significant mortality rates when compared to those in lower quartiles.

Analysis and Interpretations of Serum uric acid as an Odd for STEMI.

Table-40**. Risk factors as an Odd for Hyperuricemia.**

Risk Factors	Acute STEMI Sr uric acid			χ^2	df	Sig.	OR	95% CI	
	Hyper	Non Hyper	Total					Lower	Upper
Yes	31	14	45	12.856	1	P< 0.001	6.089	2.182	16.992
No	8	22	30						
Total	39	36	75						

The table 41 explains how far the risk factors were associated with hyperuricemia in STEMI cases. The risk factors such as Diabetes, Hypertension and DM+HT were strongly associated with hyperuricemia (P<0.001) with an Odd's ratio of 6.089.

Table-41. **Hyperuricemia as an Odd for Complications.**

Sr Uric acid	STEMI Complications			χ^2	df	Sig.	OR	95% CI	
	Yes	No	Total					Lower	Upper
Hyper	20	19	39	18.883	1	P< 0.001	17.895	3.767	85.004
Non Hyper	2	34	36						
Total	22	53	75						

The table 42 explains how far Hyperuricemia was associated with complications in STEMI. Hyperuricemia significantly correlated with complications (P<0.00) and the same was as an Odd for complications 17.895 times.

DISCUSSION

URIC ACID AND GENDER

Out of the 75 patients studied, the mean uric acid in the total population was 6.31mg/dl , of which men had higher mean uric acid level(6.74 mg/dl) when compared to women(5.49 mg/dl). But there was no statistical significance between the two groups($p>0.05$).

Similar results have been shown by Dharma et al[38] (Journal of Clinical and Experimental Cardiology, March 25,2012) in a study done in Indonesia. Similarly, a study by Nadkar et al(JAPI, Vol 56, Oct 2008)[9] has revealed no difference in uric acid levels between males and females. This is in contrast to the NHANES study (JAMA, May 10,2000) where men had significantly higher uric acid than women.

URIC ACID AND AGE

The mean age in the study group was 57.55 years in men and 66.04 years in women (figure 2).

The mean age of onset of cardiovascular event was higher in females than in males.

In our study , it was observed that uric acid levels increased with age in men but not in women (figure 3&4)

Zoppini et al (Diabetes Care, Volume 32, Sep 2009) showed similar results , where older, hypertensive men, compared to their female counterparts, had higher uric acid levels[43]. This is in contrast to the NHANES I study(JAMA 2010) and the LIFE study (Hoeiggen et al, Kidney International, Vol 65, 2004) , which showed that uric acid increased with age only in women and this association could not be found in men[45]. Nadkar et al has reported no significant association between serum uric acid and age in both genders.

The prevalence of hyperuricemia in our study was 60% in patients with STEMI, which is higher than that seen in a Thai study where it was only 49%(Vitoon et al)[36] .In the studied population, 50.77% of men and 60% of women had hyperuricemia .(figure 5)

ASSOCIATION OF URIC ACID WITH RISK FACTORS

In our study, the presence of **diabetes and hypertension** was significantly associated with hyperuricemia .(figure 21&22)

In two studies that dealt with association of acute myocardial infarction with hyperuricemia, the authors (Nadkar et al and Dharma et al) did not find any statistically significant association between these two factors and hyperuricemia. But in LIFE study that studied the effects of losartan and atenolol in hypertensive patients, there was a significant association between diabetes and hyperuricemia[45]. Similarly the NHANES study also found a significant correlation of hyperuricemia with diabetes and hypertension in both

males and females. Alexander Strasak has also showed that hypertensive subjects have slightly increased uric acid levels when compared to normotensives ,in a prospective study conducted on Austrian men[12].

Similar to many other studies, our study also shows a positive correlation between **triglyceride** level with hyperuricemia.(figure 25). But a negative correlation has been obtained with **cholesterol** levels. Li Chen et al brought out similar results with triglyceride while no association was found with cholesterol levels[10]. We also found that uric acid levels increased with increase in number of risk factors.(figure 24)

Our study did not show any positive correlation of **smoking** with hyperuricemia. (table 28)Dharma et al has shown similar results[38].

Body mass index showed no statistically significant association with uric acid levels. But it was observed that all subjects with low BMI (<23kg/m^2) had lower uric acid levels(3-5 mg/dl). As previously mentioned, South East Asian population is prone for CAD even in the presence of low BMI. Many studies done on this population have proved this effect. According to our observation, uric acid may not be useful in identifying cardiovascular risk in this subset with low body mass index. On the contrary,Zoppini et al has found significant association of uric acid levels with Body mass index[45]. But this study included only diabetic individuals, whereas our present study included a heterogenous population.

URIC ACID AND PROGNOSTIC INDICATORS

In the present study, anterior wall MI constituted about 40% of total MIs. 60% of females had inferior wall MI while 45% of males had anterior wall MI. In our study, anterior wall MI was strongly associated with hyperuricemia. But Dharma et al (JCEC,2012) found no statistically significant difference in the type of myocardial infarction associated with hyperuricemia and low uric acid levels[38]. In previous studies ,anterior location of myocardial infarction has been proved to be a poor prognostic indicator in acute myocardial infarction.

In our study, Killip Class III and IV were commonly associated with higher uric acid levels than class I and II.(figure 16). Killip class showed a linear correlation with uric acid levels.(figure 17). 8% of the subjects in the present study were in Killip class IV and hyperuricemia was found in all these patients. In a meta analysis of prognostic studies (Kojima et al,Croat MED J, March 2012),Trkulja et al has highlighted that some of the studies that compared the Killip staging with uric acid levels have brought out a strong correlation between Killip III and IV stages with higher uric acid levels, though many studies failed to match the high and low uric acid patients, in respect to the major outcome risk factors (age, Killip class or renal function)[8]. Nadkar et al has also brought out similar correlations. This result shows the prognostic significance of uric acid in ST Elevation MI.

We have found a significant association of TIMI risk score in STEMI with uric acid . Higher TIMI scores were associated with higher uric acid quartiles. Figure 18 and 19 show the relationship of TIMI scores with uric acid levels in males and females. David A. Morrow et al has proposed a bed side clinical score for prognostic assessment of fibrinolytic eligible patients with STEMI. An increase in 30 day mortality was observed in subjects with higher TIMI scores [33]more than 8. In our study hyperuricemia was significantly associated with higher TIMI scores, both in males and females.

In our study, the uric acid levels correlated well with ejection fraction.(figure 28). LV dysfunction is an important prognostic indicator in myocardial infarction. In our study, five patients had ejection fraction<30%. All patients with severe LV systolic dysfunction had uric acid levels >7 mg/dl. This result is similar to that of Li Chen et al, in their study on Japanese population. This study has also shown that persons with hyperuricemia had larger LVID[10]. But in our study, this variable was not analysed.

URIC ACID AND MACE/MORTALITY

In our study involving 75 subjects the mortality was 6.6% . All deaths occurred in males. Most of the complications occurred during the first day of presentation. One patient died on the day of admission due to arrhythmia and cardiac arrest. The other death that occurred within 3 days was due to

intracranial bleed. The other three patients had an extended hospital stay and died due to cardiac failure. It was found that the mortality in the hyperuricemic group (>7 mg/dl) was 15.15% ,while the mortality in the normal uric acid group was only 2.2%,(figure 31) which was statistically significant. The mortality in the uric acid quartile 7 – 9 mg/dl was 8% while the mortality rose to 80% in subjects with uric acid levels more than 9 mg/dl(figure32). Similar results have been observed in many studies conducted in patients with acute coronary syndromes. Nadkar et al reported hyperuricemia in all six deaths that occurred after MI. Dharma et al reported that uric acid levels >7 mg/dl was the strongest independent predictor of mortality .

The major cardiac adverse events (MACE) that occurred during the follow up were cardiac arrhythmias, most commonly ventricular tachycardia, sudden cardiac arrest, reinfarction, cardiac failure, ventricular septal rupture , papillary muscle dysfunction and intracerebral bleed. 21 of our subjects experienced one or the other complication during the course of stay in the hospital. Of these 21 patients, 15 had higher levels of uric acid on the third day, 2 subjects succumbed before the third day, and the other 6 had lower uric acid levels on the third day when compared to the day of admission. All subjects who went in for cardiac failure had higher uric acid levels on day 3. There was a significant association between the MACE and hyperuricemia. 48.72% of subjects with hyperuricemia experienced complications whereas only 5.5% of

the subjects with normal uric acid levels had complications, which was statistically significant. All subjects who had uric acid levels >7.9mg/dl experienced complications and among the 5 whose uric acid level was> 9 mg/dl, three patients succumbed. The highest uric acid level observed was 10.2 mg/dl, in a patient with ventricular septal rupture. He presented with Killip class IV and subsequently died of cardiac failure. This patient had a uric acid level of 11.2 on the third day.

Kojima et al has come up with similar results in his metaanalysis stating that hyperuricemia is associated with higher occurrence of short term and medium term major adverse cardiac events[8].

CONCLUSION

Uric acid is an old molecule with new applications and it has been studied in various metabolic diseases, pulmonary hypertension and renal failure. In this study, it has been found that uric acid has a significant correlation with age, anterior location of MI, Killip class and TIMI risk score in STEMI and also with short term adverse cardiac events and cardiovascular mortality and hence, can be considered as an independent prognostic marker in acute myocardial infarction.

LIMITATIONS OF THE STUDY

In this study, the female population was limited and hence the results cannot be extrapolated to the general population. It was only a short term prognostic study and more data will be made available if long term major adverse cardiac events are taken into account.

SCOPE FOR FUTURE RESEARCH

The role of Xanthine oxidase inhibition in the treatment of myocardial infarction and heart failure needs to be studied . Among the older drugs used in reducing cardiovascular mortality, three drugs have been proved to reduce the levels of uric acid: they are 1. Fenofibrate; 2. Statins and 3.Losartan[35] . Allopurinol has been studied on a smaller population with heart failure and long term improvements in endothelial function has been demonstrated. A significant improvement in ejection fraction and LV diameter was also observed[35]. But these results could not be extrapolated to a larger population. Large scale trials with definite end points are required to address this issue. Whether the clinical improvement is due to uric acid reduction or due to xanthine oxidase inhibition also needs to be studied.

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ANNEXURE

- **ABBREVIATIONS**
- **PROFORMA**
- **MASTER CHART**

ABBREVIATIONS

- ACC – American College of Cardiology
- ACS – Acute Coronary Syndrome
- AKI – Acute Kidney Injury
- ASMI – Anteroseptal Myocardial Infarction
- AWMI – Anterior Wall Myocardial Infarction
- BMI – Body Mass Index
- BNP – Brain Natriuretic Peptide
- CAD-Coronary Artery Disease
- CVD – Cardiovascular Disease
- DM – Diabetes mellitus
- e NOS – Endothelial Nitric Oxide Synthase
- GISSI - Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio
- GRACE - Global Registry of Acute Coronary Events
- Hs-CRP – High sensitive C Reactive Protein
- HT – Hypertension
- IHD – Ischaemic Heart Disease

- IL-6 – Interleukin 6
- IWMI – Inferior Wall Myocardial Infarction
- LBBB – Left Bundle Branch Block
- LDL – Low Density Lipoprotein
- LDL c – Small dense oxidised LDL
- Lp(a) – Lipoprotein a
- LV – Left Ventricle
- MACE – Major Adverse Cardiac Events
- MET – Metabolic equivalent
- MI – Myocardial Infarction
- MPO – Myeloperoxidase
- NO – Nitric Oxide
- NSTEMI – Non ST Elevation Myocardial Infarction
- RHD – Rheumatic Heart Disease
- ROS – Reactive Oxygen Species
- S ICAM 1- Soluble Intercellular Adhesion Molecule-1
- STEMI – ST Elevation Myocardial Infarction
- SUA – Serum Uric Acid

- TGL – Triglyceride
- TIMI – Thrombolysis In Myocardial Infarction
- UA – Unstable Angina
- URAT 1- Urate Anion Exchanger 1
- VF – Ventricular Fibrillation
- VSR – Ventricular Septal Rupture
- VT – Ventricular Tachycardia
- XOR – Xanthine Oxidoredutase

PROFORMA

NAME **AGE/SEX**

IP NO **OCCUPATION**

WINDOW PERIOD

SYMPTOMS

RISK FACTORS

- **Diabetes**
- **Systemic Hypertension**
- **Smoking**
- **Alcoholism**
- **Family H/O CAD**

8. PAST HISTORY

- **Chronic drug intake**
- **Known CAD**
- **H/O ATT**
- **H/O Chronic Kidney Disease**
- **H/O Hypothyroidism**
- **Presence of myeloproliferative diseases**

9. CLINICAL EXAMINATION FINDINGS

- **PULSE RATE**
- **BP**
- **JVP**
- **BASAL CREPTS**
- **S3 GALLOP**

❖ **ECG IN ALL LEADS:**

❖ **TYPE OF MI:**

❖ **KILLIP CLASS:**

❖ **THROMBOLYSIS:**

❖ **HEIGHT: WEIGHT: BMI:**

❖ **TIMI SCORE:**

10. INVESTIGATIONS

a) Blood Sugar

b) Blood Urea

c)Serum Creatinine

d) Total Count: ; Differential count:

e) Hemoglobin

f) Erythrocyte Sedimentation Rate

g) Serum Cholesterol

h) Serum Triglyceride

i) Serum Uric Acid on day 1:

on day 3:

j) Ejection Fraction:

10. HOSPITAL STAY:

11. COMPLICATIONS

12. MORTALITY:

Sl No	NAME	AGE	SEX	WINDOW	PR	BP	KILLIP	TYPE	DM	HTN	SMOKING	FAMILY	no of risk	CHOL	TGL	BMI	TIMI	UA 1	UA 2	EF	COMPL	STAY	MORTALI
1	MUTHURAJ	75	M	2.5	104	160/90	I	AW	Y	Y	N	N	2	182	158	22.7	8	7.4	6	40.8	N	10	N
2	ACHIAMMAL	65	F	3	72	140/90	I	AS	Y	N	N	N	1	186	191	24.7	4	6.3	6.2	42	N	7	N
3	SAMIKANNU	60	F	4	62	120/80	I	IW	N	N	N	N	0	192	154	25	0	5.4	5.6	48	A	8	N
4	HARIKRISHNAN	52	M	2.5	60	130/80	II	AW	N	Y	N	N	1	173	126	21.78	4	7.2	5	38.5	N	12	N
5	GANAPATHY	53	M	2	72	120/80	I	AS	Y	N	Y	N	2	182	152	23.82	2	5.9	4.2	42.5	N	7	N
6	THANGAIYAH	47	M	5	88	150/70	I	AS	N	Y	Y	N	2	119	112	20.1	4	6.9	5.2	40	N	10	N
7	PALRAJ	40	M	3	78	120/90	I	IW	N	N	N	N	0	96	116	21.2	0	4.4	5	44	N	6	N
8	PETCHIMUTHU	75	M	2	80	130/90	I	AW	Y	N	N	N	1	140	124	23.61	5	7.1	6.2	41.4	N	6	N
9	SURESH	37	M	4	72	130/80	I	IW	N	N	Y	Y	2	184	151	21.73	0	4.3	4.2	46.6	N	7	N
10	PREMKUMAR	24	M	4	80	130/90	I	AW	N	N	Y	Y	2	172	86	23.78	1	5.1	5	40.4	N	8	N
11	PARAMANAND	66	M	1	100	160/90	II	AW	N	Y	N	N	1	185	110	23.2	8	8.1	8.3	36.8	F	6	N
12	SIVAN PANDI	46	M	5	78	130/80	I	AW	N	N	Y	N	1	192	154	24.76	2	6.9	5.6	42.8	N	6	N
13	PARVATHY	50	F	3	88	110/70	I	AS	N	N	N	N	0	184	140	24.5	1	5.2	4.9	44.2	N	5	N
14	KRISHNAN	45	M	2	82	150/100	I	IW	N	N	Y	N	1	176	142	23.43	0	4.3	5	43	N	6	N
15	VINCENT	38	M	2	98	130/90	I	AS	N	N	Y	Y	2	303	1272	33.12	1	5.9	5.2	43.8	N	8	N
16	HABEEB MOHD	66	M	6	110	100/80	IV	AW	Y	Y	Y	Y	3	202	164	24.83	9	10.2	11.8	25	VSR	7	Y
17	GNANA DURAI	55	M	5	78	130/80	I	AS	N	N	Y	N	1	156	136	23.33	2	4.4	4.3	44.3	N	6	N
18	ESAKKIMUTHU	67	M	7	120	180/120	III	AW	N	Y	Y	N	2	213	185	29.76	9	8	8.7	34.8	FT,F	7	N
19	ADHINARAYANA	45	M	1	62	130/80	I	IW PW	Y	N	N	Y	2	227	224	32.7	1	5.3	5.1	49.6	N	6	N
20	MOHD UZHAIM	58	M	2	86	170/90	II	AW	Y	Y	N	N	2	177	121	22.14	4	7.8	7.2	39.8	N	7	N
21	SHANKARASUBU	54	M	2	86	150/80	III	LW PW	Y	N	Y	N	2	213	272	26.22	3	6.4	5.8	42.5	N	9	N
22	PARAMASIVAN	72	M	5	32	100/80	III	AW	N	Y	Y	N	2	92	182	23.7	7	10	10.8	26	CHB VSR	8	Y
23	ANNAMALAI	65	M	6	120	100/70	III	LBBB	Y	N	N	N	1	394	154	24.87	9	8.6	8.8	31.7	F	12	N
24	SAHASRANAMAM	65	M	3	100	140/90	II	AW	Y	N	Y	N	2	191	272	23.8	7	7.5	6.2	39.4	VT	7	N
25	VEL THEVAR	60	M	6	108	60/?	IV	IW	N	N	Y	N	1	167	132	23.86	8	7.6	7.3	35.9	VT	10	N
26	KADARKARAI	75	M	4	80	130/80	I	AW	Y	N	Y	N	2	198	194	24.4	5	10	-	-	ICH	3	Y
27	AYYAPPAN	35	M	3	84	100/80	I	IW PW	N	N	N	Y	1	130	88	24.82	1	3.8	3.4	49.8	N	6	N
28	RAMESH	58	M	5	72	150/100	II	AW	N	Y	Y	N	2	234	212	30.33	5	7.6	7.4	39.2	A	7	N
29	GOPAL	59	M	5	82	140/90	II	AW	N	Y	Y	N	2	163	226	24.56	6	7.5	9.6	30	R,S	14	Y
30	MURUGAN	55	M	3	100	160/90	II	AW	Y	Y	Y	N	3	167	108	23.54	5	7.6	5.8	37.2	N	7	N
31	SHENBAGAVALLI	48	M	4	104	150/100	I	AW	N	Y	N	N	1	183	139	23.08	4	7.2	6.7	48.4	N	6	N
32	KALIAMMAL	55	F	6	76	170/60	I	IW	Y	Y	N	Y	3	227	140	26.8	2	5.2	5.4	50	N	7	N
33	PUSHPAM	65	F	8	120	120/70	I	AW	Y	Y	N	N	2	176	156	20.76	7	6.8	6.1	39.4	N	12	N
34	LAKSHMI	65	F	3	82	140/90	I	AS	N	N	N	N	0	232	155	27.54	3	6.2	6	412	N	7	N
35	GNANA DURAI	55	M	5	78	130/90	I	AS	N	N	Y	N	1	156	106	22.87	2	4.2	3.6	42.3	N	6	N
36	DHIRAVIYAM	70	M	5	80	120/80	I	AW	N	N	N	N	0	139	111	23.7	4	6.7	5	38.5	N	8	N
37	MAHARAJAN	25	M	7	86	140/80	I	AW	N	N	Y	Y	2	218	197	24.26	2	6.7	5.2	40.8	N	7	N
38	AKKAMMAL	60	F	1	58	130/90	II	IW/RV/PW	N	N	N	N	0	188	190	24.71	2	6.5	6	42	N	10	N
39	AYYAKANNU	72	M	4	82	90/60	II	IW/PW	N	N	Y	N	1	205	253	23.6	7	7.8	5.2	46	N	8	N
40	SANGILIKALAI	70	M	6	80	50/?	IV	AW	Y	N	N	N	1	186	105	22.89	9	8.4	8	32	VT	10	N
41	MANJULA	38	F	4	98	140/90	I	IW/RV	Y	N	N	Y	2	148	117	22.92	1	4.2	4	56	N	5	N
42	SAKTHIVEL	62	M	5	98	140/70	I	AW	N	N	N	N	0	162	145	23.8	2	6.1	5.8	40	N	6	N
43	RAMAIAH	58	M	3	82	130/70	II	IW	N	N	Y	N	1	202	156	28.45	2	5.4	5.1	52	N	7	N
44	MEERAN	65	M	5	98	80/50	IV	AW	N	Y	Y	N	2	234	187	22.89	9	8.2	10.2	26	FT,VT,F	14	N
45	MUTHU KUMAR	60	M	4	82	120/70	I	IW	Y	N	N	N	1	187	167	23.32	1	4.2	4.3	42	N	7	N
46	SRINIVASAN	56	M	6	100	170/100	I	AW	N	Y	Y	N	2	156	123	23.13	3	6.8	5	35.8	N	6	N
47	VELAYUTHAM	54	M	4	108	150/70	II	LBBB	Y	Y	N	N	2	198	156	23.54	7	8.2	8.5	34	F	6	N
48	SHEIKH	62	M	6	98	140/70	I	AW	N	Y	Y	N	2	208	187	25.43	3	6.9	5.6	42	N	8	N
49	VEERASAMY	65	M	4	72	130/80	I	AW	N	N	Y	N	1	176	145	25.89	4	6.8	5	38.7	N	6	N
50	ARUNACHALAM	59	M	6	88	150/80	I	IW	N	Y	N	N	1	167	132	22.34	2	5.6	4.2	52	N	6	N
51	JEYASEELAN	63	M	5	108	100/60	III	AS	Y	Y	N	N	2	228	234	31.3	7	7.9	8.4	39	F	10	N
52	PODUMPONNU	68	F	4	32	90/60	III	IW/RV/PW	N	N	N	N	0	176	210	22.21	7	7.1	6.2	44	N	7	N
53	MADHAVAN	56	M	6	110	130/70	II	AS	Y	N	Y	N	2	189	167	28.67	7	7.3	7	40	N	8	N
54	MARKANDAN	60	M	3	82	140/70	I	IW	N	Y	N	N	1	178	146	20.25	1	4.2	4	43.7	N	7	N
55	SATHYAMOORTH	68	M	4	98	180/90	II	AS	N	Y	N	Y	2	187	124	25.67	6	7	5.4	42	N	7	N
56	JESURAJ	55	M	3	80	130/80	I	IW PW	N	N	Y	N	1	163	134	23.89	0	5.2	4.8	39.7	N	6	N
57	MOOKAN	67	M	4	108	150/70	III	LBBB	N	Y	Y	N	2	212	152	26.56	8	9.2	9.3	37	F	8	N

58	SYED ALI	59	M	6	64	80/60	IV	IW RV PW	Y	Y	Y	Y	4	256	312	29.84	7	7.3	5.4	41	N	7	N
59	MURUGAN	49	M	3	88	130/70	I	AS	Y	N	N	N	1	162	190	27.91	2	5.8	5	39	N	6	N
60	MANIKANDAN	55	M	5	32	60/40	IV	IW PW	N	N	N	Y	1	139	198	28.12	6	7.9	6	45.9	CHB	7	N
61	GANAPATHY	60	M	6	92	140/80	I	IW	N	N	N	N	0	162	149	27.86	2	5.1	4	42	N	8	N
62	VENKATESAN	55	M	3	58	100/60	I	AS	Y	N	N	N	1	176	125	29.13	2	6.4	6.5	40	N	9	N
63	KALIAPPAN	67	M	5	108	90/60`	III	AW	Y	N	Y	N	2	190	178	26.74	12	8.8	9.7	24	F	12	N
64	GOMATHINAYAG/	71	M	6	110	150/90	II	AS	N	N	Y	N	1	264	213	27.23	8	9.2	9.8	31	AKI, F	9	N
65	NARAYANAN	75	M	2.5	104	160/110	I	AW	Y	Y	N	N	2	186	154	23.7	8	7.4	7.9	36.8	F	10	N
66	MEENAMMAL	68	F	4	68	140/100	I	IW	Y	N	N	N	1	176	121	23.7	4	6	6.2	42	N	7	N
67	RAJAVEL	60	M	4	62	120/80	I	IW	N	N	N	N	0	192	124	23.58	0	4.4	4.2	48	N	8	N
68	CHOKKALINGAM	52	M	2.5	60	130/80	II	AW	N	Y	N	N	1	173	126	24.2	4	7.2	5	38.5	N	12	N
69	CHANDRASEKAR	53	M	2	72	120/80	I	AS	Y	N	Y	N	2	182	132	23.8	2	5	4.2	42.5	N	7	N
70	KANDEEPAN	62	M	6	102	110/70	II	AS	N	N	Y	N	1	119	172	22.62	6	6.4	8.2	37	A	10	N
71	MANOHAR	40	M	3	78	120/90	I	IW	N	N	N	N	0	108	126	22.52	0	4.5	4	44	N	6	N
72	VELAYUTHAM	75	M	2	80	130/90	I	AW	Y	N	N	N	1	140	124	23	5	7	6.2	37.4	N	6	N
73	DILIP KUMAR	42	M	4	72	130/80	I	IW	N	N	Y	Y	2	184	121	21.82	0	4.2	4.2	46.6	N	7	N
74	ENAMUTHU	70	M	5	110	130/90	II	AW	Y	N	Y	Y	3	172	186	24.78	9	8.8			VT,A	1	Y
75	SAKTHIVEL	59	M	6	99	120/70	II	AS	N	Y	Y	N	2	187	174	23.98	5	7	7.2	39	N	10	N